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RADIOACTIVE DRUGS AND RADIOACTIVE BIOLOGICAL PRODUCTS

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[Docket No. 75N–0067]

RADIOACTIVE NEW DRUGS AND RADIOACTIVE BIOLOGICS

Termination of Exemptions

In a notice of proposed rule making published in the FEDERAL REGISTER of July 29, 1974 (39 FR 27538), the Commissioner of Food and Drugs proposed to terminate the present exemption for radioactive new drugs (including radioactive biological products) for investigational use from new drug requirements and classify, by use, radioactive drugs either as "new drugs" or as generally recognized as safe and effective for their intended use and therefore not "new drugs" when used under the conditions specified. Interested persons were invited to submit comments on the proposal by September 27, 1974.

The Commissioner of Food and Drugs is terminating the present exemption for radioactive drugs, including radioactive biological products, from the investigational new drug requirements of the Federal Food, Drug, and Cosmetic Act. The Food and Drug Administration (FDA) is establishing regulations to assure that after August 25, 1975 all radioactive drugs, except those for certain research uses, introduced into interstate commerce are subject to a "Notice of Claimed Investigational Exemption for a New Drug" (IND), an approved new drug application (NDA), or a biological product license. In addition, the FDA is establishing regulations setting forth specific conditions under which radioactive drugs for certain research uses, other than clinical trials to determine safety and effectiveness, are not subject to the new drug requirements of the act.

The Commissioner, for the purpose of an orderly development of regulations relating to the establishment of procedures for codifying old drug monographs for prescription drugs which are generally recognized as safe and effective and not misbranded, has redesignated proposed new 21 CFR Part 370 as 21 CFR Part 361 and limited it to drugs used in research. All future old drug monographs for such drugs will be incorporated into Part 361.

The U.S. Nuclear Regulatory Commission (NRC), a new agency created by Pub. L. 93–438 and Executive Order 11834, assumed the licensing and related regulatory responsibilities of the former Atomic Energy Commission (AEC) on January 19, 1975. To conform to this organizational change, all references to the AEC in this regulation and in the preamble have been changed to the NRC. In the quotation from and discussion of comments received from members of the public on this proposed regulation, references to the AEC have been changed to the NRC even though the comments from the public were made prior to the organizational change.

Elsewhere in this issue of the FEDERAL REGISTER the Commissioner is issuing an order effecting a transfer of responsibility for radioactive biological products from the Bureau of Biologics to the Bureau of Drugs.

Comments on the proposal were received from 21 different sources; namely, hospitals, universities, professional organizations, trade associations, manufacturers, Agreement States (i.e., States which, under formal agreement with the NRC, are authorized to license, under Federal law, persons engaged in the possession, use, or transfer of reactor-produced radionuclides in their respective states), and State health departments.

The major areas of concern as expressed by the comments were the composition of the Radioactive Drug Research Committee (proposed as the Radiation Safety Committee), the use of State advisory committees, radiation dosimetry, procedures for providing the summary of information on radioactive drugs for investigational use and the "Report on Research Use of Radioactive Drug" to the NRC and appropriate Agreement States, limitation on pharmacological dose for research not under an IND, and the applicability of the proposed regulation to radiopharmacies. Eight comments supported the proposal in principle but offered suggestions for modification, clarification, and addition to some areas. The principal comments received and the Commission's conclusions are as follows:

DEFINITION OF A RADIOACTIVE DRUG

1. One comment pointed out that in § 312.1 the additional information to be supplied in new items 6.d, 10.a, and 16 of Form FD–1571 is required only if the investigational drug is a "radioactive drug" but the term "radioactive drug" is not defined in the proposed regulation.

The Commissioner has determined that a "radioactive drug" is any substance defined as a drug in section 201 (g) (1) of the Federal Food, Drug, and Cosmetic Act which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance. The term "radioactive drug" includes a "radioactive biological product" as defined in 21 CFR 600.3(ee). This definition does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. Section 310.3 has been amended to include this definition in paragraph (n).

IND REQUIREMENTS FOR RADIOACTIVE NEW DRUGS

2. Several comments suggested that the Summary of Information as required by § 312.1 be forwarded directly by the manufacturer to the NRC or Agreement States rather than by the Food and Drug Administration. Such a procedure would enhance the manufacturer's efforts to protect the confidentiality of any proprietary information contained in the summary, would free the FDA from further administrative workload, and would eliminate the possibility of administrative delays in forwarding the necessary information to the NRC or Agreement States. Comments also pointed out that the proposed regulation does not provide a procedure for notifying the NRC and Agreement State authorities that the FDA has approved an NDA or issued a biological product license.

This proposed regulation was not intended to preclude the sponsor from forwarding the Summary of Information directly to the NRC or Agreement States. The proposal was merely a service which FDA would provide to IND sponsors and to the Federal and State licensing agencies to expedite the processing of licensing applications. The Summary of Information serves no regulatory purpose for the FDA. Failure of the IND sponsor to submit the Summary of Information, or to authorize its release to licensing agencies, would not alter the status of the IND.

The Commissioner had intended that the release of the Summary of Information to Federal and State licensing bodies would not waive any confidentiality to which the sponsor of the IND would be entitled under the FDA Public Information regulations (21 CFR Part 4; 21 CFR 312.4; and 21 CFR 314.14). Under these regulations, FDA records which are normally exempt from disclosure (e.g., existence and contents of an IND) may be disclosed, without requiring disclosure to the public at large, to a department or agency that has concurrent jurisdiction over the matter and separate legal authority to obtain the specific information involved, 21 CFR 4.84. The NRC (and through it, the Agreement States) would satisfy these criteria. The regulations require, however, that such disclosure "be pursuant to an agreement that the record shall not be further disclosed by the other department or agency except with the written permission of the Food and Drug Administration." The NRC has informed the FDA that it would not agree to this restriction and would not assure any confidential treatment for the Summary of Information.

The Commissioner believes that, under these circumstances, retaining the Summary of Information would not be justified because the administrative problems which would arise are too numerous. First, separate agreements would be required for each of the 25 Agreement States; besides the practical difficulties involved, the legality of these agreements would be in doubt, since the Agreement States derive authority from the NRC. Secondly, each IND submission with a Summary of Information would have to be examined to determine in which states the IND drug might be used; those with agreements for confidentiality would be notified, but those without, and those under NRC jurisdiction, would not be notified. In short, providing this service would become very complicated. One alternative, to provide that an explicit waiver of confidentiality be signed by the IND sponsor if he chose to submit the Summary of Information, seemed unlikely to generate a significant num-

ber of cases in which FDA could disclose the Summary of Information. It might also confuse sponsors and lead to erroneous or unintended waivers.

Therefore the Commissioner has deleted item 16 from the proposed amendments to IND Form FD–1571 and item 6.i and item 4.i from the proposed amendments to Forms FD–1572 and FD–1573, respectively. The Commissioner advises that he remains quite willing to adopt a procedure for providing information regarding IND's directly to Federal and State agencies if and when all such agencies agree not to disclose any confidential information so provided without the written permission of the FDA.

The Commissioner advises that the FDA has notified Agreement States and the NRC of all existing approved NDA's and biological product licenses for radioactive drugs and radioactive biological products. Procedures have been established to continue to notify the NRC and all Agreement States of all new approvals of NDA's for radioactive drugs and radioactive biological products. These procedures do not, however, preclude an applicant from notifying the NRC or an Agreement State of an NDA approval.

3. One comment suggested that § 312.1 should include concise and complete details for an acceptable protocol and pointed out that such areas as dosimetry, expected or documented clearance rates, and rationale of diagnosis or therapy were not contained in the new proposed rules.

The Commissioner is of the opinion that the present IND regulations (§ 312.1) and Form FD–1571 with the additions set forth in the proposal, are adequate as requirements for the development of a protocol for producing well-controlled clinical data on radioactive drugs. Each protocol for an IND study for a radioactive drug wil be evaluated individually. In § 312.1, item 10.a of Form FD–1571 requires that the protocol include studies which will obtain sufficient data for dosimetry calculations and that these studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material. The FDA is currently preparing guidelines for research protocols on radioactive drugs; the Radioactive Pharmaceuticals Advisory Committee is assisting in this and, as drafts are developed, they will be discussed in open sessions of that advisory committee. When adopted, these guidelines will be available from the Agency.

4. One comment questioned whether it was necessary to amend or otherwise alter an existing IND for a nonradioactive investigational new drug if the drug is "tagged" with a radioactive element in accordance with the limitations set forth in proposed §370.100. The comment also expressed the opinion that, if an investigational drug is "tagged" and administered at or near a pharmacologic dose, the new information required in items 6.d and 10.a of Form FD–1571 should be submitted as an amendment to the existing IND and a new IND should not be required.

The Commissioner concludes that it is not necessary to amend an existing IND for a nonradioactive investigational new drug if the drug is "tagged" with a radionuclide in accordance with the limitations set forth in § 361.1 (proposed § 370.100), and the specific research study is within the purposes set forth by that section. The results of the research study using the "tagged" compound must, however, be submitted to the existing IND. If pharmacological data are not sufficient to permit compliance with the requirements of § 361.1, it would of course be necessary to submit a new IND or, preferably, to amend the existing IND for the nonradioactive investigational new drug to conduct a study on the drug "tagged" with a radionuclide, even though the radioactivity limits set forth in § 361.1 are met. To amend an IND in this way, the information required in items 6.d and 10.a of Form FD–1571 must be submitted.

5. One comment suggested that, to assist the Federal and State regulatory agencies in fulfilling their responsibility for licensing the use of radioactive materials, the Summary of Information required in Form FD–1571 should be expanded to include: information describing the plan of investigation in sufficient detail to permit a critical evaluation of the methods and controls to be used; an indication as to whether any complementary drug or radionuclide administration is planned or contemplated in conjunction with the study; an indication of the expected fate of the radiopharmaceutical administered; if for therapeutic purposes, an indication of the expected effects; and calculations of the radiation doses delivered to the whole body and to the critical organ(s).

As stated in paragraph 2 above, the Commissioner has deleted item 16 (Summary of Information) from the amendments to IND Form FD–1571. Information needed by the NRC and Agreement States for licensing purposes must be obtained from the IND sponsors.

6. One comment suggested that, although radiopharmaceuticals are relatively simple organic compounds with little or no toxicological/pharmaceutical activity and may not require chronic toxicity studies, the regulations should require semichronic toxicity studies in anticipation that radiopharmaceuticals may, in the near future, be considerably more complex.

The Commissioner recognizes that an IND for radioactive drugs may in some cases require chronic or subacute toxicity studies. The preamble to the proposed regulations only noted that chronic toxicity studies may not be required for some radioactive drugs. The requirements for any IND will depend on the specific nature of the drug and its proposed uses.

7. One comment argued that the proposed regulations failed to distinguish between "hot" (radioactive) and "cold" (nonradioactive) pharmaceuticals and between diagnostic and therapeutic agents by applying to radioactive pharmaceuticals the same clearance procedures applicable to nonradioactive pharmaceuticals. The comment further suggested that a definitive statement was needed recognizing the difference between these two types of pharmaceuticals, as well as clear guidelines setting forth a workable format from which manufacturers can fashion their studies to comply with investigational new drug as well as new drug application requirements. These guidelines should be specifically tailored to reflect realistically the unique problems in the field of radiopharmaceuticals.

The Commissioner realizes that IND requirements for radioactive drugs will differ in various ways from those involving nonradioactive drugs, and this is clearly stated in the preamble to the proposed regulations. This situation is not unique, however, since requirements for one nonradioactive drug may differ sharply from those for a different nonradioactive drug. The requirements of § 312.1 are general requirements and are regularly adapted as appropriate for specific drugs. The FDA is currently in the process of drafting guidelines for conducting clinical trials involving radioactive drugs.

NDA Requirements for Radioactive New Drugs Generally

8. One comment questioned whether or not a mechanism had been established for filing abbreviated new drug applications for diagnostic radiopharmaceuticals.

The Commissioner advises that no mechanism has been established yet for submitting an abbreviated new drug application for a radioactive drug. The Commissioner recognizes, however, that the amount of clinical data necessary to approve an NDA varies among radioactive drugs, depending on several factors. Applicants are invited to meet with representatives of the FDA, Bureau of Drugs, Division of Oncology and Radiopharmaceutical Drug Products, to discuss the amount of data needed prior to submission of an NDA.

9. One comment suggested that there be a mechanism whereby previous work performed under an IND or an NDA could be referenced for a radiopharmaceutical for which a new use is being developed, provided the previous work is applicable to the new use.

The Commissioner advises that previous unpublished studies relating to a radioactive drug for which a new use is being developed may be incorporated by reference from one IND or NDA file into another only if the sponsor of the previous IND or applicant of the previous NDA authorizes the new sponsor or applicant to use these data.

NDA Requirements for Certain Radioactive New Drugs

10. One comment indicated that, at the outset of the preamble to the proposal, a statement is made that "any radiopharmaceutical which is not a 'new drug,' i.e., when used under the conditions specified, will require neither an IND nor an NDA, but will require certain documentation to establish that the drug is in fact being

used under the conditions set forth in the regulation." The proposed rules then go on to set dates for the filing of an NDA for all radioactive pharmaceuticals with well-established medical uses. The comment requested clarification as to how those pharmaceuticals listed in § 310.503 (f) (1) relate to those referred to above.

The Commissioner advises that § 310.503(f) (1) lists a group of new drugs, reactor-produced radionuclides and their chemical forms, which the FDA and the NRC have determined have well-established medical uses. In view of the extent of experience with drugs containing these radionuclides, the FDA and the NRC have concluded that they should not be distributed under investigational use labeling when they are actually intended for use in medical practice. Such drug products have not been used to a material extent or for a material time and are not yet regarded as generally recognized as safe and effective for their labeled indications. However, it may reasonably be expected that adequate evidence of safety and effectiveness can be submitted by manufacturers and distributors for use of these drugs as recommended in appropriate labeling. In order to continue shipping in interstate commerce drugs containing these radionuclides, manufacturers and distributors must submit an NDA, IND, or application for a biological product license, on or before August 25, 1975. An IND will not, however, permit continued commercial marketing of these drugs.

On the other hand, § 361.1 (proposed as § 370.100) specifies conditions under which radioactive drugs are generally recognized as safe and effective and therefore are not new drugs. Such drugs do not require an NDA, biological product license, or IND. The statement quoted in the comment referred to the fact that, for these drugs, reports will be required (in the form of annual or special reports from the Radioactive Drug Research Committee (see paragraph 29)) to assure FDA that use of the drug remains within the conditions under which the drug is generally recognized as safe and effective.

11. One comment questioned whether the December 31, 1974 deadline for submission of NDA's applies only to those radioactive drugs listed in "§ 130(c) of the November 13, 1971 FEDERAL REGISTER" and in the table included in § 310.503(f) (1) of the July 29, 1974 proposal.

The Commissioner assumes that the comment meant to refer to "§ 130.49(c) in the FEDERAL REGISTER of November 3, 1971" instead of "§ 130(c) in the FEDERAL REGISTER of November 13, 1971." The December 31, 1974 deadline set forth in the July 29, 1974 proposal for submission of an NDA, IND, or application for a biological product license applies only to drug products, including biological products, which contain any of the radionuclides listed in § 310.503(f) (1) in the "Chemical form" listed and for the indications listed. This deadline has now been extended to August 25, 1975. The purpose of this deadline is to allow manufacturers and distributors who are currently marketing drug products containing any of the radionuclides listed in § 310.503(f) (1) time to submit to the FDA information necessary for continued marketing of these products. This deadline is not applicable to drug products, including biological products, containing any of the radionuclides listed in § 310.503(c) (formerly § 130.49(c)). Manufacturers and distributors were given until March 3, 1972 to submit an NDA, IND, or application for a biological product license to continue distribution of those products for any of the indications listed.

12. One comment pointed out that the November 1971 regulations allowed the submission of a new drug application for an existing product without requiring the prior submission of either clinical data or an investigational new drug application and questioned whether such a policy was still in effect.

The Commissioner advises that this policy is applicable to those radioactive drugs listed in § 310.503(f) (1). These are products which the FDA and the NRC consider to have well-established medical uses. The Commissioner has concluded that manufacturers and distributors of these drugs may reasonably be expected to be able to submit adequate evidence of safety and effectiveness for use as recommended in appropriate labeling without conducting additional clinical studies to obtain such data. The policy is the same as that announced in the November 3, 1971 order for similar radioactive drugs.

13. One comment stated that this proposal "would create a new structure, on a temporary basis, to regulate a relatively small number of drugs." The comment further stated that "it may be more effective to require immediate submission of an IND and to permit the drug's continued use in interstate commerce for a shorter period under the same circumstances as it had been thereto used."

The Commissioner assumes that the comment is in reference to § 310.503 which lists a group of new drugs, reactor-produced radionuclides and their chemical forms, which the FDA and the NRC determined have well-established medical uses. No new structure is proposed to deal with these drugs. In view of the extent of experience with the radionuclides listed in § 310.503(f) (1), the FDA and NRC concluded that they should not be distributed under investigational use labeling when they are actually intended for use in medical practice, and that manufacturers and distributors may reasonably be expected to submit adequate evidence of safety and effectiveness for use as recommended in appropriate labeling. To continue shipping drugs containing these radionuclides in interstate commerce an NDA, IND, or application for a biological product license, must be submitted. An IND will not, however, permit continued commercial marketing of these drugs.

14. One comment requested clarification as to what effect, if any, the revision of § 310.503 would have on lists of "well-established uses" which many Agreement States have developed but which do not totally agree with those of the NRC. Another comment proposed the addition of Indium-113m to the list in § 310.503(f) (1).

The Commissioner has determined that only those radioactive drugs listed under § 310.503 shall be considered by the FDA to have well-established uses in medical practice. In the preamble to the proposal, the Commissioner invited any person who believed that other radioactive drugs are widely used in medical practice and should be added to this list to submit comments and data proposing and justifying the addition of such drugs. The request for addition of the isotope Indium-113m to the well-established list was submitted. The data submitted in support of the request (which is on display in the Hearing Clerk's office) have been reviewed, the Radioactive Pharmaceuticals Advisory Committee consulted, and the request approved. Section 310.503(f) (1) has been modified accordingly.

15. A comment requested that the regulations for radioactive new drugs include provisions to clarify the requirements regarding reactor-produced byproduct materials when such products are processed and shipped in bulk to other manufacturers for reprocessing into finished drug forms.

The Commissioner advises that bulk byproduct materials intended for processing, repacking or use in the manufacture of another drug shall be processed, shipped, and labeled in compliance with 21 CFR 201.122 (formerly 21 CFR 1.106 (1)).

NUCLEAR PHARMACY ISSUE

16. One comment questioned whether the FDA had jurisdiction over radioactive drugs, in the investigational stage or for well-established medical uses, that are prepared by the using physician and qualified associate staff rather than procured from a commercial pharmaceutical concern. The comment further stated that the provision of nuclear medicine services and the continued development of techniques, methods and products would be severely inhibited by requiring an IND or NDA under such circumstances, particularly in the larger clinical and research centers where much of the innovative and developmental advances evolve. Another comment questioned whether the proposed regulation was applicable to those so-called "regional radiopharmacies" which manufacture their own radioactive drugs including the non-radioactive components.

Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is issuing a notice regarding the Food and Drug Administration's policy on the "nuclear pharmacy" issue.

REQUIREMENTS FOR RESEARCH USES OF RADIOACTIVE DRUGS GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

A. SCOPE OF DETERMINATION

17. One comment stated that in medical institutions operating under an NRC Broad Medical License new radiopharmaceuticals are sometimes developed in-

ternally and subjected to clinical trials to establish diagnostic or therapeutic efficacy. The comment questioned whether it is necessary for these institutions to submit an IND even though in the developmental and testing phase the drug is not shipped in interstate commerce. The comment further questioned whether such clinical trials relating to diagnostic efficacy were covered by proposed § 370.100 and whether it would be necessary to file reports on investigators of this type approved by a radioisotopes committee under a Broad License, either annually or immediately. If such clinical trials are not covered by proposed § 370.100, would the dose restrictions specified under that section apply?

The Commissioner advises that the FDA has jurisdiction over all drugs, including radioactive drugs, shipped in or introduced into interstate commerce whether prepared by a medical institution, physician, or a commercial drug manufacturer. "Shipment in interstate commerce" is determined not only by the interstate shipment of the final dosage form of the drug product, but also by the interstate shipment of the components of the drug product, as well as other factors. Therefore, where a determination is made that interstate commerce is involved (also see paragraph 16 of this preamble), an IND must be submitted before the drug product may be used in clinical trials.

As stated in the preamble to the proposal, the Commissioner has concluded that the provisions of § 361.1 (proposed § 370.100) are not applicable to clinical trials intended to determine the safety and/or effectiveness of a radioactive drug. Section 361.1 only applies to research "intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry but not intended for immediate therapeutic, diagnostic, or similar purposes." Clinical trials using new radioactive drugs are subject to the requirements of an IND as set forth in § 312.1. Section 361.1 of this regulation has been clarified to reflect this. The dose restrictions set forth in § 361.1 do not apply to clinical trials conducted under § 312.1.

18. One comment expressed confusion in interpreting the scope of the exemption provided by proposed § 370.100 as it relates to the development of new radioactive diagnostic agents. The comment further stated that it was not clear why the particular agent being studied cannot be used specifically for diagnostic purposes if the criteria for exemption under proposed § 370.100 are met (i.e., radiation safety, pharmacological inactivity, and Radioactive Drug Research Committee approval).

Section 361.1 (proposed § 370.100) provides for the use of tracer amounts of radionuclides, attached to various compounds, in research studies to obtain basic information on drug metabolism, specific physiologic or pathophysiologic processes in humans, and the kinetics, distribution, and localization of the various "tagged" compounds. Certain studies included in this category may be essential parts of the development of a new diagnostic agent (for example, studies conducted to determine where the radioactive drug is localized or the extent to which it is concentrated in certain organs or tissues). Such studies fall within the scope of § 361.1 if other requirements of that section are met. These studies must be distinguished from studies intended to evaluate the safety and effectiveness of a radioactive drug as a diagnostic agent. In this case the drug is used, not as a research tool, but as a new diagnostic agent for which safety and effectiveness must be proven; therefore, there is no basis for concluding that it is generally recognized as safe and effective as a diagnostic agent. The radioactive diagnostic agent, therefore, must be studied under an IND.

B. LIMITS ON PHARMACOLOGICAL DOSE

19. Several comments were received regarding the requirements under the proposed § 370.100 that the pharmacological dose shall be known not to cause any clinically detectable pharmacological effect in human beings. One comment expressed the thought that such a limit on the pharmacological dose was unrealistic and unnecessary and would place severe and unnecessary restrictions upon research in such vital areas as human drug metabolism. The comment further noted that, since doses known not to cause any clinically detectable pharmacological effect are often substantially below the therapeutic dose, radioactive studies conducted with such minute doses would not be representative of the pharmacokinetics of the drug studied at the therapeutic dose. Further, it was stated that such studies would not furnish enough labeled metabolites to conduct metabolite studies. Another comment suggested that the exemption from IND requirements should include the tagging of a drug at a dose level having a pharmacologic effect if that dose level is safe and effective, as evidenced by an approved NDA.

In the preamble to the proposed regulation, the Commissioner made it clear that for radioactive drugs to be considered not new drugs for certain uses it was necessary to conclude that they were generally recognized as safe for such uses. The Commissioner suggested that such a conclusion could certainly be reached, with regard to the pharmacological safety of the drug, if the drug was known not to produce clinically detectable pharmacological effects on the basis of data from studies in human beings. If such data are not available, even the smallest amount of that drug must be assumed to produce pharmacological activity. Once pharmacological activity is known or assumed to occur, pharmacological safety cannot be presumed and other evidence of general recognition of safety is necessary. Without this evidence, the drug is considered to be a new drug, and any research with it must meet the requirements of § 312.1, including the submission of an IND.

The fact that a drug is approved for certain specific uses means that it is considered safe and effective for these uses. It is not considered safe and effective for other uses or for non-therapeutic uses. The Commissioner recognized that the proposed standard for demonstrating general recognition of safety (i.e., the absence of pharmacological activity) was a strict standard and interested persons were invited to submit comments on the appropriateness of the proposed standard. While proposing this standard, the Commissioner also invited comments on an alternative test; namely, that the amount of radioactive drug administered not exceed a dose of 10 percent of the lowest single dose recommended by the drug's labeling, or in the absence of approved labeling, 10 percent of the lowest single dose recommended by recognized medical texts, with the exact dosage being reviewed by a peer committee for safety. Although comments objected to the proposed standard and, in some cases, suggested alternatives, no comments were received which provided reasons for considering any standard, other than the absence of clinically detectable pharmacological activity, as demonstrating general recognition of safety. While the Commissioner may at some future time reconsider this issue, he has concluded that, at present, for the purpose of this regulation, general recognition of pharmacological safety can be considered to exist only when the drug has no clinically detectable pharmacological effect in human beings.

It should be stressed that it is not anticipated that there will necessarily have been a formal dose-response study that defines the lower threshold dose for a clinically detectable pharmacological effect. For example, if the circulating blood levels or excretion rate of an endogenously produced substance is well known, it may be possible for the Radioactive Drug Research Committee (see paragraph 29) to conclude that some small fraction of these levels or rates (e.g., administration over a given interval of a low percentage of the amount of a substance that is produced endogenously during the same interval) represents an amount without detectable pharmacological effect. Or, if large amounts of a substance such as an amino acid or sugar are regularly consumed as foodstuffs, it may be possible for the Radioactive Drug Research Committee to conclude that a small amount of it (e.g., a small percentage of the amount usually consumed during a meal), at least by the oral route, would be without detectable pharmacological activity.

The Commissioner is aware that pharmacokinetic studies or studies requiring isolation of metabolites may require larger amounts of a drug. Such studies may either be conducted under an IND or in persons already receiving the nonradioactive drug for a therapeutic purpose.

20. One comment suggested modification of proposed § 370.100(b)(2) to allow, under well-defined conditions, the administration of the radio-labeled ver-

sion of a pharmacological agent when this pharmacological agent is administered to the patient in pharmacological doses as part of a therapeutic treatment and to assess the effectiveness of that particular therapy. The comment suggested adding the statement "If a drug is used under protocol for therapeutic purposes, then a minimal dose of the radio-labeled isomer of this drug can be added to help evaluate the radiopharmacokinetics of this drug."

The Commissioner advises that this regulation in no way restricts the use of a nonradioactive drug, i.e., under an IND, NDA, or old drug status, whether or not the radioactively labeled version of this drug is administered at the same time to evaluate the pharmacokinetics of the drug. For such a study to be permitted under § 361.1, the conditions of that section must be met, except that in this case the limitation on pharmacological dose will be such that the aggregate amount of the drug administered (nonradioactive drug and tagged compound) shall be known to remain an appropriate dose for the use for which the nonradioactive drug is being given. The regulation has been clarified to reflect this. The Commissioner also advises that if the nonradioactive drug has an IND, the results of any research studies using the radioactively labeled version of the drug and performed under § 361.1 must be included as part of the required IND reports.

21. One comment stated that the fundamental information to determine what "traditional pharmacology based judgment" means needed amplification and the term "no response" was not clear.

In paragraph D.1 of the preamble to the proposal, the Commissioner stated that "when radioactive drugs are administered in amounts which have been demonstrated not to produce clinically detectable pharmacologic activity in human beings, such drugs are and must be generally recognized as safe from the viewpoint of traditional pharmacology." In this context "traditional pharmacology" was intended only to distinguish hazards related to the toxic effects of the drugs (traditional pharmacology/toxicology) from those related to hazards of radiation. The term "clinically detectable pharmacologic activity" in human beings has been discussed above. Neither the term "no response" nor "traditional pharmacology" are used in the regulation; therefore no change is needed.

C. LIMITS ON RADIATION DOSE

22. One comment indicated that the intent of proposed § 370.100(b)(3) was not clearly stated in the preamble but presumed that the radiation limits are stated so that it will not be necessary to file an IND for research projects which do not lead to diagnostic tests.

The Commissioner advises that the intent of § 361.1 (proposed § 370.100) is to identify a class of drugs that are not new drugs because they are generally recognized as safe and effective under specific circumstances. One of those circumstances is that the radiation dose to subjects does not exceed certain limits. The identification of this drug class as not new drugs has the effect of making it unnecessary to submit an IND before using them.

23. One comment questioned whether it was necessary that there be a radiation dose limit included among the conditions under which the use of radioactive drugs for research is considered safe and effective. The comment stated that "if a local committee is deemed to have the judgment to assess and approve varied lesser dose procedures, need they be limited in regard to the far less frequent situations of a particularly important research study that might necessitate a larger organ dose?" The comment suggested that it might be preferable to offer the option to the local committee of referring to an FDA-sponsored "supercommittee" research proposals which, because of larger dosage or other unusual considerations, the local committee would prefer to have acted upon by a higher authority.

The Commissioner disagrees with the suggestion of the comment. When a pharmacologically inactive amount of a radioactive drug is used, the issue of safety for use in human subjects is entirely related to the amount of radiation administered. Because any exposure to radiation is presumed to have an attendant risk (due to a lack of evidence showing any absolutely safe level of exposure), it is obvious that no radiation exposure can be justified or considered generally recognized as safe as a research tool if the study in which it is used is of poor quality or is not likely to provide useful information. The Commissioner has concluded that the Radioactive Drug Research Committee (see paragraph 29) can assure the quality of studies and the minimization of the radiation dose. Nevertheless, despite this conclusion, the Commissioner has no basis for concluding that all doses of a radioactive drug, even if used for research purposes and monitored by a properly functioning committee, are generally recognized as safe for the intended use. He has therefore concluded that a limit on radiation dose is necessary to make a determination of general recognition of safety for research uses. As discussed below (in paragraph 24), the Commissioner has concluded that the basic occupational radiation protection criteria established by the NRC under 10 CFR 20.101 and 20.102, even though they were not intended to be criteria related in any way to subjects in clinical research, provide a reasonable basis for the determination that a radioactive drug, when administered in amounts such that the pharmacological and radiation dose from such drug is within the limits of § 361.1(b), and under the cognizance of an FDA-approved committee, is generally recognized as safe. It should be emphasized that this limit for purposes of establishing general recognition of safety in no way represents a conclusion that such radiation doses do not represent some element of risk to the individual nor that larger doses are necessarily unsafe. It is further emphasized that setting a limit on radiation dose for purposes of § 361.1 does not alter the requirement that the radiation dose, even though it is within the limit, should be the smallest amount needed to carry out the study. It is only concluded that, within the context of the benefit to be obtained from the research study, that such radiation doses are generally recognized as safe. Radioactive drugs which deliver larger doses are considered to represent new drugs and to require an IND or approved NDA.

24. One comment questioned whether it was appropriate to use the occupational permissible exposure criteria as a limit upon the approval authority of the proposed Radiation Safety Committee (under proposed § 370.100(b)(3)) since such limits were developed for a specific purpose and should not be extended to research use of radiation in human volunteer subjects.

As stated in the preamble to the proposal, the Commissioner fully agrees with the National Council on Radiation Protection and Measurements who, in discussing radiation dose to research subjects, noted that "each proposed human research application must be judged on its merit after review by competent peers, and that dose-limiting recommendations for radiation workers or the public do not apply to the individual to be irradiated." The Commissioner concludes that § 361.1 of this regulation embodies this recommendation and requires that each study be approved by competent peers (the Radioactive Drug Research Committee) and that the radiation dose be kept as low as practicable. The radiation dose criteria in § 361.1(b)(3) are for the purpose of stating that such research studies are generally recognized as safe and not to set a specific dose limit for research subjects.

The Commissioner referred, in the preamble to the proposal, to various studies and published literature which reflect a consensus which permitted the establishment of exposure levels acceptable from the standpoint of radiation safety. The NRC criteria, set forth in 10 CFR 20.101 and 20.102, accord with this consensus.

The NRC requirements take into account both the risk to the public health of larger doses of radiation for a particular group of persons and the risk to the individuals involved. Investigational subjects, like radiation workers, represent a limited segment of the total population; the public health implications of doses of radiation to research subjects appear no different from those resulting from exposure of radiation workers and the risks are equally acceptable to society. Considerations of risk to the individual also appear reasonably similar for both groups. An informed potential research subject is able to make a decision regarding participation in a study because he will, in effect, be deciding whether or not he is willing to participate in the study and assume a risk in the same sense as does a radiation worker. Although the benefits to the individual are quite different, in one case the opportunity to earn a livelihood, in the other the opportunity to participate in a scientific study, each situation in-

volves a decision to take a specified risk for a specified purpose. The Commissioner concludes that these doses represent a minimal risk to the individual and are appropriate criteria for a general recognition of safety where there are societal benefits from research studies.

25. One comment expressed the opinion that use of the occupational radiation exposure limitation (as an upper limit for exposure of research subjects in studies covered by proposed § 370.100) is too high in comparison with the intended scope of the studies.

The Commissioner notes that it is probable that many studies under § 361.1 (proposed as § 370.100) can be carried out using smaller doses of radiation than would be permitted under the limits on radiation dose. As noted earlier, it is the responsibility of the Radioactive Drug Research Committee (see paragraph 29) to assure that the smallest dose that can be used without jeopardizing the study is used. The Commissioner believes that doses up to the limits set forth in § 361.1 and used under conditions specified in that section can be considered generally recognized as safe and effective and constitute a reasonable limit for research studies conducted under this section. The Food and Drug Administration will continually evaluate the use of radioactive drugs under § 361.1 through the review of the required annual reports submitted by the Radioactive Drug Research Committee. The present criteria for establishing a radiation dose limit will be reconsidered if justified by this evaluation.

26. Several comments questioned the particular radiation dose limits selected. One comment suggested that it would be preferable to state any limitation as a maximum organ dose in any one year with the further qualification that in the event of a very long effective half-life situation, the total dose over the life expectancy of the concerned subject would not exceed some considered value. Another comment stated that it was not clear how the yearly cumulative total for whole body exposure for adults and the yearly total for critical organs were derived.

The Commissioner has reconsidered the proposed maximum radiation doses in light of the comments above and further intra-agency discussion. As originally proposed, maximum yearly doses were given. To provide adequate protection for subjects in special circumstances where long half-life radionuclides are used, the wording has been changed so that there will be both an annual limit on dose received and a limit on the total dose commitment resulting from studies conducted in a single year. Thus, the regulation has been modified to include both the "annual dose" and "total dose commitment" from a study or studies conducted within a single year. In addition, maximum whole body dose and the dose to critical organs (active blood-forming organs, lens of the eye, and gonads) have been made identical. The proposed notice specified limitations for "critical" organs that should have been applied to other organs. This has been corrected in the final order. As modified, the total dose commitment to any research subject, from a single study or cumulatively from a number of studies within a single year may not exceed the total commitment value of 5 rems for exposure to the whole body and critical organs (active blood-forming organs, lens of the eye, and gonads) or 15 rems for exposure to other organs. The designation of whole body, critical organs, and other organs within the various dose categories has been modified in the regulation to conform to terminology used by the NRC.

It is further recognized that significant radioactive contaminants or impurities in a radioactive drug may affect the results of a study or alter the validity of the dose calculations; therefore, any contribution to dose due to significant radioactive contaminants or impurities shall be included in calculating the total radiation dose and dose commitment. In addition, in determining maximum permissible dose limitations, the possibility of followup studies shall be considered for inclusion in the dose calculations. Section 361.1(b)(3) (proposed as § 370.100(b)(3)) has been revised accordingly.

27. One comment raised a question regarding the relationship between exposure history and the radiation limitations. The comment stated that the repeated reference to occupational exposure limitations in proposed § 370.100 (b)(3) and (d)(1) appear to sanction a quarterly occupational exposure of 3 rems. The comment further stated that this level of exposure is allowed in Agreement State and NRC regulations only with a properly completed exposure history and that there is no provision for an exposure history in the proposed regulation. The comment did not object to the 3 rems limit but to the use of such phrases in the proposed § 370.100 as "occupational exposure limitations" and "absorbed dose * * * permissible for occupationally exposed personnel."

The Commissioner believes that the limitations on radiation dose have been clarified in the final order. With the addition of an annual dose, an indication of a quarterly radiation dose is unnecessary. It is thus clear that, with a total annual dose of 5 rems for whole body and critical organs, 3 rems cannot be administered in each quarter.

"Exposure history," as required under NRC and Agreement State regulations, refers to previous occupational exposure. The Commissioner is of the opinion that very few research subjects will have been radiation workers and therefore they will not have an "exposure history." The Commissioner advises that, in revising paragraph (b)(3) and (d)(1) of § 361.1 of the regulation, the phrases "occupational exposure limitations" and "absorbed dose * * * permissible for occupationally exposed personnel" have been deleted.

28. One comment expressed concern that some research programs may also involve radiation doses from radiographic or fluoroscopic procedures such that the total subject dose may exceed the occupational permissible dose limits. The comment further stated that the x-ray dose may or may not be totally or partly of direct diagnostic benefit to the concerned subject or may or may not be part of medical care that the subject would receive if not volunteering for the study. The comment requested clarification as to whether any limitations on radiation dose to the subject that may be set under proposed § 370.100(b)(3) are applicable only to the dose attributable to the radionuclide procedure or only to the dose attributable to the research aspect of the subject's radiation experience during the period of concern, or to some other dose calculation. The comment expressed the opinion that it is not practicable to attempt to set regulatory limits based on the total radiation experience associated with a research use of radioactivity, because of the many considerations involved in assessing the value-risk ratio of an individual research proposal.

The Commissioner advises that the radiation dose limitations under § 361.1 (b)(3) (proposed § 370.100(b)(3)) are the total doses attributable to the research study including the radioactive drug and any doses from x-ray procedures which are considered and integral part of the research study, i.e., would not have occurred but for the study. An x-ray procedure which would have occurred whether or not the patient was part of the research study should not be included in determining the doses attributable to the research study. The Commissioner considers the determination of whether or not a given x-ray procedure is a part of the patient's medical care, as opposed to part of the research procedure, to be one which the Radioactive Drug Research Committee (see paragraph 29) can readily make.

D. RADIOACTIVE DRUG RESEARCH COMMITTEE

29. Comment was received from the Nuclear Regulatory Commission (NRC) requesting that the term Radiation Safety Committee as used in § 361.1 be changed to Radioisotope Research Committee or any other appropriate name. The NRC stated that the term Radiation Safety Committee is used by many hospitals and academic institutions for the committee that reviews the institution's overall program for use of radioactive materials and radiation producing machines, especially from the standpoint of radiation protection which is frequently called health physics.

The Commissioner has therefore concluded that, to distinguish between this committee and the committee required for approval of research uses of radioactive drugs under § 361.1 of this regulation, the term "Radiation Safety Committee" as used in § 361.1 shall be changed to "Radioactive Drug Research Committee." The regulation has been modified accordingly. In stating the following comments and their discussion, the revised committee name is used.

30. One comment recommended that the field of pharmacology be included as a discipline to be considered for repre-

sentation on a Radioactive Drug Research Committee under the proposed § 370.100(c)(1). Other comments expressed the feeling that a pharmacologist should be a required member of such committee. Comments also differed as to whether a radiopharmacist should be included in the membership of the Radioactive Drug Research Committee. Some comments indicated that there may be some misunderstanding as to who the required members of a Radioactive Drug Research Committee are.

The Commissioner concludes that the composition of the Radioactive Drug Research Committee as set forth in § 361.1(c)(1) is adequate. As stated in the proposed regulation, approval of a Radioactive Drug Research Committee shall be based upon an assessment of the qualifications of the members of the committee and the assurance that all of the necessary fields of expertise are covered. Certification in a particular discipline is not necessary. For example, one of the required members of the Committee shall be a person qualified to formulate radioactive drugs. This person need not necessarily be a radiopharmacists; he may be a physician or other qualified individual. The Commissioner also sees no reason to specify additional disciplines as required members because § 361.1(c)(1) states that the addition of consultants in other pertinent medical disciplines is encouraged. Expertise in any needed area can thus be obtained. The Commissioner advises that the only three required fields of specialization of a Radioactive Drug Research Committee are (1) a physician recognized as a specialist in nuclear medicine, (2) a person qualified by training and experience to formulate radioactive drugs, and (3) a person with special competence in radiation safety and radiation dosimetry. The remaining members shall be selected from individuals qualified in varied disciplines pertinent to the field of nuclear medicine (e.g., radiology, internal medicine, clinical pathology, hematology, endocrinology, radiation therapy, radiation physics, radiation biophysics, health physics, and radiopharmacy). Section 361.1(c)(1) has been rewritten to indicate more explicitly the required members.

31. One comment pointed out that the proposed § 370.100(c) gave no guidance regarding notification of changes in the membership of the Radioactive Drug Research Committee (e.g., because of relocation, retirement, or death of members) and the effect of such changes upon FDA approval of the Committee. The comment suggested that such changes be reported and documented in the annual report and that approval or disapproval of the revised Committee be determined by the FDA following receipt of the annual report.

The Commissioner has studied the comment and concludes that all changes in the membership of the Radioactive Drug Research Committee and selection of new members shall be communicated to the FDA as early as possible so that the FDA may review the qualifications of the new member(s) and the composition of the Committee and be assured that the Committee continues to include all of the necessary fields of expertise. Section 361.1(c)(4) (proposed § 370.100(c)(4)) has been revised to provide for this procedure. The Commissioner advises that once a Radioactive Drug Research Committee is approved, it continues in such status until the approval is withdrawn by the FDA. Individual changes in membership may therefore be implemented without FDA approval; FDA disapproval of a new member would take the form of withdrawal of approval of the Committee.

32. One comment expressed concern over the proliferation of duplicative committees deriving their authority from various Federal and State regulatory agencies. It recommended that FDA limit, at least initially, those committees which it approves pursuant to proposed § 370.100(c)(4) to those already established medical advisory committees of radioactive material licensing agencies and the radiation safety committees of broad medical licensees of the NRC. Another comment expressed concern that the FDA might not approve a Radioactive Drug Research Committee which has been approved as a Broad License Committee by an Agreement State or the NRC, or vice versa, and suggested that there be some criteria for mutual acceptance of a Radioactive Drug Research Committee. The comment further questioned whether the regulation would allow the Medical Committee of a State Radiation Advisory Board to review and approve research programs for small user licensees.

The Commissioner has determined that, to conclude that a radioactive drug is generally recognized as safe and effective when used for certain research studies, it is necessary to establish criteria for use of the drug which include a monitoring of that use by a Radioactive Drug Research Committee. The standards for the composition and functioning of the Radioactive Drug Research Committee are a fundamental element in the Commissioner's determination. The Commissioner cannot assume that the requirements for advisory or review committees of other Federal or State regulatory agencies will assure a committee that meets FDA criteria for a Radioactive Drug Research Committee. Therefore the FDA cannot, without an independent determination, approve a Committee that has been approved by another Agency. However, any established committee, such as the Medical Committee of a State Radiation Advisory Board, may, if constituted in accordance with § 361.1(c)(1), apply to the FDA for approval as a Radioactive Drug Research Committee.

33. One comment questioned the need for each Radioactive Drug Research Committee to meet at least quarterly, as provided in proposed § 370.100(c)(2), because the quantity of business to be considered by the Committee may not justify such frequent meetings.

The Commissioner concurs in part and has concluded that the Radioactive Drug Research Committee shall meet at least once each quarter in which a research activity has been authorized or conducted. No more than 90 days should pass between the start of the research and the monitoring of the study's progress by the Committee. More frequent meetings may be held at the discretion of the Committee.

The Commissioner has also determined that to provide reasonable assurance that the expertise available within the committee will be utilized in committee deliberations, it is necessary to indicate the number of members needed to constitute a quorum. He has concluded that more than 50 percent of the membership of the Committee must be present to constitute a quorum and that there must be appropriate representation of the required fields of specialization. Section 361.1(c)(2) (proposed as § 370.100(c)(2)) has been revised accordingly.

34. One comment expressed the opinion that more efficient use of the concept of a Radioactive Drug Research Committee as a "watchdog body" in cases of experimental use of radioactive drugs should be to expand its function to cover both new and not new radioactive drugs.

The Commissioner advises that review of investigations of new radioactive drugs submitted pursuant to § 312.1 is clearly a regulatory function of the Food and Drug Administration and cannot be delegated to a Radioactive Drug Research Committee. Institutional review is also required for investigational new drugs under an IND where the clinical studies are conducted on institutionalized subjects or are conducted by an individual affiliated with an institution which agrees to assume responsibility for the study. The Radioactive Drug Research Committee would not fulfill this requirement because its composition lacks lay membership. The FDA would, however, look favorably upon a Radioactive Drug Research Committee serving as a subcommittee of an Institutional Review Committee when the Investigational new drug is a radioactive drug. The Commissioner advises that this regulation does not in any way prohibit an institution from involving its Radioactive Drug Research Committee in other policy matters, including use of radioactive new drugs, if it so chooses.

35. One comment suggested that, because of the inherent time delays involved in obtaining protocol review and approval from a Radioactive Drug Research Committee as envisioned by the regulations, and because of the relatively short shelf life of many of the tagged drugs utilized, the regulations include a maximum time limit within which the Committee would have to approve or reject a proposed protocol.

The Commissioner concludes that regulation of the time required for approval or rejection by a Radioactive Drug Research Committee of a proposed protocol must be left to the institution or State or Federal agency with which the Committee is associated. The Commissioner cannot predict the workload of each Radioactive Drug Research Com-

mittee; therefore, it is not feasible for the FDA to establish a time frame for review and approval or rejection of a proposed protocol. The FDA believes, however, that since the Radioactive Drug Research Committee is composed of persons familiar with the unique problems of research with radioactive drugs, committee review will be responsive to the needs of individual researchers. The Commissioner further assumes that ordinarily approval of a protocol will be sought before the tagged drug is obtained; therefore, the shelf life of the tagged drug will not be germane.

36. Several comments suggested that the "Report on Research Use of Radioactive Drug" which each Radioactive Drug Research Committee is required to submit annually under proposed § 370.100(c)(3) for each study conducted during the preceding year be made available to Agreement States or other licensing agencies for future licensing actions without forfeiting the nondisclosure provisions which apply to proprietary information. Another comment suggested that FDA consider establishing some mechanism of advising its approved Radioactive Drug Research Committees of any studies which have been approved under proposed § 370.100 by any other approved Radioactive Drug Research Committee.

The Commissioner advises that contents of the "Report on Research Use of Radioactive Drug" are available for public disclosure unless confidentiality is requested by the investigator and it is adequately shown by the investigator that the report constitutes a trade secret or confidential commercial information as defined in 21 CFR 4.61. A trade secret, as defined in 21 CFR 4.61, may consist of any formula, pattern, device, or compilation of information which is used in one's business and which gives him an opportunity to obtain an advantage over competitors who do not know or use it. Commercial information that is privileged or confidential means valuable data or information which is used in one's business and is of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs. Data and information submitted or divulged to the Food and Drug Administration which fall within the definitions of a trade secret or confidential commercial information are not available for public disclosure.

The note under "Report on Research Use of Radioactive Drug" set forth in proposed § 370.100(c)(3), stated that the name of the investigator would not be disclosed publicly. Under the new regulation promulgated under the Freedom of Information Act, such information may be publicly disclosed. Section 361.1(c)(3) (proposed § 370.100(c)(3)) has been revised accordingly.

Therefore, information from this report which is available for public disclosure is also available to Agreement States or other licensing agencies and all Radioactive Drug Research Committees and will be disclosed in accordance with procedures set forth in 21 CFR Part 4. The Commissioner has concluded that it is impractical, because of resource limitations, to provide these reports to Agreement States and other licensing agencies and to other FDA Radioactive Drug Research Committees on a continuing basis. A specific request will be required under the public information regulations (21 CFR Part 4).

37. One comment recommended that the age of all research subjects, not just minors, be included in the "Report on Research Use of Radioactive Drug" set forth in proposed § 370.100(c)(3). Another comment suggested that the number of adults and children be specified separately on each report.

While such data are not necessary to monitor compliance, the Commissioner concludes that data such as the age and sex of all research subjects would be useful in evaluating the total risk to the public health and to individuals. Further, the Commissioner notes that this data would be useful to the FDA in studies of the radiation dose to the public from all radioactive drugs. Accordingly, § 361.1(c)(3) of the regulation has been modified to require the "Report on Research Use of Radioactive Drug" to include the dose to each research subject by age and sex.

38. One comment objected to the requirement of reporting immediately when more than 30 research subjects were involved in a research project under proposed § 370.100 since the individual risks to a human subject receiving radioactive materials are independent of the number of subjects. Another comment felt that annual reporting by the Radioactive Drug Research Committee and their function as a peer review group were sufficient and therefore objected to immediate reporting as stated above or when the research subject is under 18 years of age.

The Commissioner wishes to be certain that the requirements of § 361.1 (proposed § 370.100) are being interpreted and followed in a satisfactory manner. Relatively large research studies, such as those resulting in the exposure of more than 30 research subjects, represent a category of study in which it may be particularly appropriate to examine whether the need for the number of subjects chosen is documented, the radiation dose is well justified, and the distinction between research protocols and clinical trials is observed. Similarly, any study involving radiation exposure to research subjects less than 18 years of age may need special attention to examine the basis for carrying out the study in that age group and assure that the protocol is adequate for the safety of such subjects. The Commissioner emphasizes that the early notification of FDA under these circumstances in no way implies that such studies are unacceptable or inappropriate or that these studies require preclearance by the FDA. Notification is entirely for FDA's internal monitoring of this new regulation.

39. One comment suggested that item 5 of the "Report of Research Use of Radioactive Drug" be revised to read as follows:

5. Radiation Absorbed Dose:
a. Radionuclide identification.
b. Administered activity dose—child, adult (max.).
c. Maximum number of activity doses per patient.
d. Estimated absorbed dose per single procedure—whole body, gonad and critical organ.

The Commissioner has reviewed the terminology in item 5 and is of the opinion that the requirements should be stated in more specific terms. He has therefore revised these parts of the "Report of Research Use of Radioactive Drug" to read as follows:

5. Name of the radionuclide(s) used, including any present as significant contaminants or impurities.
6. Radiation absorbed dose. Give the methods by which radiation dose commitment was estimated, such as by calculation, by in vivo measurements, by uptake excretion, or by other methods. For each subject, provide:
a. Age, sex.
b. Amount of each radionuclide administered.
c. Estimated absorbed dose per single administration of radioactive drug, expressed as whole body, active blood-forming organs, lens of the eye, gonads, and other organ dose.
d. If more than one administration of a radioactive drug per subject, cumulative radiation dose and dose commitment, expressed as whole body, active blood-forming organs, lens of the eye, gonads, and other organ doses from the administered radionuclides.

E. OTHER CONDITIONS

40. Three comments expressed the opinion that proposed § 370.100(d)(1) should require the radioassay of the pharmaceutical prior to administration and one comment suggested that the use of a dose calibrator be required. One comment assumed that a dose calibrator would be required.

Although proposed § 370.100 implies that the radioactive drug will be assayed prior to use, this is not stated explicitly. The Commissioner therefore concurs with this part of the comment, concluding that radioassay of some kind is necessary prior to use of the radioactive drug. Specific designation of a dose calibrator is inappropriate, however, since other assay methods would be acceptable. Section 361.1(d)(1) (proposed § 370.100(d)(1)) is therefore amended to require radioassay of the radioactive drug prior to its use.

The Commissioner advises that § 361.1(d)(1) has also been amended to state more specifically the requirements which the Radioactive Drug Research Committee must consider to assure that the radiation dose to research subjects is as low as practicable to perform the study and to meet the criteria set forth in § 361.1(b)(3). To help achieve this assurance, two additional requirements have been added to this paragraph; namely, that the radioactive drug chosen for the study has that combination of half-life, types of radiation, radiation

energy, metabolism, chemical properties, etc., which results in the lowest dose to the whole body or specific organs with which it is possible to obtain the necessary information and that the investigator utilize adequate and appropriate instrumentation for the detection and measurement of the specific radionuclide.

41. One comment stated that proposed § 370.100(d)(5) appeared to prohibit research studies involving metabolism during pregnancy and felt that the acceptability of performing a specific study on pregnant females should be the decision of the FDA-approved Radioactive Drug Research Committee.

Both the International Commission on Radiological Protection (ICRP) and the National Council on Radiation Protection and Measurements (NCRP) have expressed concern over the possible adverse effects on the human embryo and fetus from radiation exposure to pregnant women. The Commissioner has determined that, because of the potential risk to an embryo or fetus, the use of a radioactive drug during pregnancy cannot be generally recognized as safe; therefore, such studies cannot be conducted under § 361.1. This limitation in no way reflects, however, any prejudgment as to whether such a study may be conducted under an IND. The Commissioner emphasizes that the radiation dose limits, pharmacological dose limits, Radioactive Drug Research Committee requirements, and all other requirements of § 361.1 relate only to a specific group of radioactive drugs for certain research uses. There is no intent that any of these limits represent actual or de facto limits for studies conducted under an IND. Therefore, research studies in pregnant women may be permitted where the sponsor submits an IND and complies with the requirements of § 312.1.

42. One comment requested clarification of proposed § 370.100(d)(7) as to whether the statement in "No study involving * * *, no matter how small the amount of radioactivity, shall be permitted * * *." would require Radioactive Drug Research Committee approval for the use of any compound containing naturally occurring radioisotopes such as potassium which contains 0.012 percent K–40.

The Commissioner advises that § 361.1 (proposed § 370.100) pertains only to compounds to which tracer quantities of certain radionuclides have been deliberately attached and not to an element, such as potassium, which contains trace amounts of radioisotopes in its natural state. Section 361.1(d)(7) has been modified to reflect this.

43. One comment questioned the meaning of the word "active" as used in the term "active ingredient," relative to information required on the label by section 502(e) of the act and proposed § 370.100(f) and expressed the feeling that all ingredients in an injectable preparation should be specified and listed under proposed § 370.100(f) and a determination made later on whether they are "active" or not.

The Commissioner advises that the definition of "active ingredient" in 21 CFR 210.3(d)(5) (formerly 21 CFR 133.1(d)(5) prior to recodification published in the FEDERAL REGISTER of March 27, 1975 (40 FR 13996)) is applicable to § 361.1(f)(4) of these regulations. Active ingredient is defined as "any component which is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term shall include those components which may undergo chemical change in the manufacture of the drug and be present in the finished drug product in a modified form intended to furnish the specified activity or effect." The Commissioner agrees that radioactive drug products intended for parenteral administration under § 361.1 should be labeled to identify all inactive ingredients in the same way as other drug products for parenteral administration under § 201.100(b)(5)(iii) (formerly § 1.106(b)(2)(v)(c)) and has modified § 361.1(f) correspondingly. All other label requirements imposed by section 502 (b) and (e) of the act which were stated in the preamble to the proposal have also been listed under § 361.1(f).

The Commissioner also advises that the proposal (in the preamble and proposed § 370.100(f)) indicated label and labeling requirements for radioactive materials. Such requirements are specific label requirements as imposed by section 502 (b) and (e) of the act and certain other requirements and are to appear on the label of the immediate container and shielded container unless otherwise specified. The wording in the final order has been revised to reflect this.

44. One comment suggested revising paragraph (f) of proposed § 370.100 to read: "A radioactive drug prepared, packaged, distributed and primarily intended for use in accordance with the requirements of this section shall be exempt from section 502(f)(1) of the act and section 1.106 of this chapter if the packaging, label and labeling are in compliance with Federal, State, and local law regarding radioactive materials and if the packaging, label and labeling required for radioactive materials by the Nuclear Regulatory Commission and by State and local radiological health authorities bear the following: * * *." The comment further proposed the addition of a new paragraph (f)(6) to read "whether the drug is for investigational use only;" and a new paragraph (f)(7) to read "The expiration date, special storage conditions, pyrogenicity, specific concentration and addition of bacteriostatic agents" and addition of a new sentence reading "In the event that the immediate container of any radioactive drug is too small to contain the information set forth in paragraph seven (7) above, the information shall be furnished in the product's accompanying label."

The Commissioner concludes that the initial wording of § 361.1(f) (proposed § 370.100(f)) is preferable to the suggested alternative. The requirements by the FDA for labeling may be in addition to the requirements of the NRC, other Federal authorities, or State and local radiological health authorities. Paragraph (f) of proposed 370.100 was therefore written to allow the NRC or the State and local health authorities to decide whether they wanted a distinct radioactive warning on the label, apart from other labeling. The suggested alternative does not provide for this.

The suggested paragraph (f)(6) is not applicable since these are not investigational drugs, as that term is normally used (i.e., a drug under an IND), although these drugs are used for research. The statement described in § 361.1(f)(2) is proper for radioactive drugs for research use under this section.

With regard to the suggested paragraph (f)(7), the name and quantity of all bacteriostatic agents and other inactive ingredient(s) are required by 21 CFR 201.100(b)(5)(iii) (formerly 21 CFR 1.106(b)(2)(v)(c)) if a drug product is for parenteral use. Section 361.1(f) (proposed 370.100(f)) has been modified to include this requirement. Section 502(h) of the act requires that drugs liable to deterioration shall bear a statement of such precaution as necessary for the protection of the public health. The Commissioner concludes that, because of the special nature of radioactive drugs, i.e., radioactive decay, the label for such drugs shall contain an expiration date. If special storage conditions are necessary to maintain the drug product's stability for its anticipated shelf life, manufacturers are responsible for providing such information in the labeling. If a radioactive drug is recognized in an official compendium, it shall be labeled as prescribed by such compendium.

Current good manufacturing practices require that the manufacturer assure that the drug finished dosage form has the identity, strength, quality, and purity stated in the labeling. For radioactive drugs for parenteral use, manufacturers must therefore have evidence that the methods of manufacture and sterilization employed are adequate to ensure that each final product is sterile and pyrogen free. It is the responsibility of the Radioactive Drug Research Committee to determine that radioactive materials for parenteral use under § 361.1 are prepared in sterile and pyrogen-free form.

The Commissioner has also concluded that the specific concentration for each radioactive drug should be expressed on the label. Section 361.1(f) (proposed § 370.100(f)) has been revised to require that the label include the total quantity of radioactivity in the drug product's immediate container and the amount of radioactivity per unit volume or unit mass at a designated referenced time. Section 361.1(f) has also been revised to require that the label bear the route of administration if the drug is for other than oral use, as is required for all prescription drugs under 21 CFR 201.100. Information which may be placed on the label of the shielded container only if

the immediate container label is too small to accommodate all of the necessary information is also specified.

MISCELLANEOUS

45. One comment suggested changing paragraph (b) of proposed § 370.100 to read: "The conditions under which use of any radioactive drug for research, which has been, are now or will be regulated by the Food and Drug Administration or which is introduced into interstate commerce, as safe and effective are:". The comment also suggested adding a new paragraph (d) to proposed § 370.100 to state "These regulations will not act to exempt any drug covered by this part from any other provision of law or regulation applicable thereto."

The Commissioner has concluded that the suggested changes to proposed § 370.-100 are unnecessary. This regulation in no way implies that other provisions of law or regulation are not applicable. In fact, the regulation clearly alludes to the licensing requirements of the NRC. This regulation will apply to all radioactive drugs that are generally recognized as safe and effective until future developments, experience, or knowledge necessitates revision.

46. One comment stated that there were no recommendations in the proposed regulations pertaining to the proper disposal of isotopes.

The Commissioner advises that the NRC and Agreement States control radiation safety during the manufacture, use, and disposal of radioactive drugs.

47. One comment asked if a separate office within the FDA had been assigned responsibility solely for radiopharmaceuticals.

The Commissioner advises that for all radioactive drug products, including radioactive biological products, review of a "Notice of Claimed Investigational Exemption for a New Drug," amendments to such notice, a new drug application, amendments and supplements to such application, and approving and monitoring the activities of the Radioactive Drug Research Committee shall be the responsibility of the Radiopharmaceutical Group, Division of Oncology and Radiopharmaceutical Drug Products, (HFD-150), Bureau of Drugs, 5600 Fishers Lane, Rockville, MD 20852. Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is issuing an order transferring responsibility for radioactive biological products from the Bureau of Biologics to the Bureau of Drugs to consolidate processing of all radioactive drug matters in one office.

48. One comment indicated that proposed § 370.100(f) permits the label and labeling of "tagged" compounds to contain information required by the NRC or State authorities, but this is not mentioned regarding those radioactive drugs covered under topics A, B, and C of the preamble to the proposal.

The Commissioner has determined that all radioactive drugs, including those which require the submission of an NDA, IND, or an application for a biological product license, as discussed under topics A, B, and C of the preamble to the July 29, 1974 proposal, are permitted to have on their label and labeling information required by the NRC and State and local radiation control authorities, if all of the FDA labeling requirements of section 502 of the act and 21 CFR 201.100 (formerly 21 CFR 1.106(b)) are met.

49. One comment expressed concern as to the effect these regulations will exert on existing competition within the radiopharmaceutical industry during the transition from regulation by the NRC to regulation by the FDA. Further, the comment expressed concern regarding the cost of the transition and any competitive disadvantage or restrictions imposed during this transition period. The comment emphasized that it is essential that nothing in these regulations create a competitive advantage for one manufacturer over another.

The Commissioner sees no basis for the concern expressed by the comment.

50. Two comments pointed out a typographical error in the paragraph heading for proposed § 1.106(p). The word "radiocative" should read "radioactive."

The typographical error as noted in the comment has been corrected. In addition, proposed § 1.106(p) has been recodified as § 201.129 in the final regulation in accordance with the recodification of § 1.106 into Part 201, published in the FEDERAL REGISTER of March 27, 1975 (40 FR 13996).

EFFECTIVE DATES

51. One comment requested that the December 31, 1974 and July 1, 1975 deadlines as set forth in the proposal be extended by the FDA on a drug-by-drug and manufacturer-by-manufacturer basis to provide adequate time to comply with the final regulations, following any any modification resulting from comments submitted.

The proposal identified effective dates for specific changes to implement FDA regulations regarding radioactive new drugs. Due to the length of time needed to review the comments and prepare the final regulation, the Commissioner has found it necessary to extend these proposed effective dates as follows: (1) the December 31, 1974 date for submission of an NDA, IND, or an application for a biological product license for each drug containing those radionuclides listed under § 310.503(f)(1) and for submission of the information for an investigational new drug as required by § 310.503(g) is extended to August 25, 1975; (2) the October 1, 1974 date referred to in § 310.-503(g) is extended to July 25, 1975; (3) the January 1, 1975 date referred to in § 310.503 (f) (4) and (5) and (h) is extended to after August 25, 1975; (4) the effective date for deleting the "Note" that appears at the end of § 312.1 is extended to after August 25, 1975; and (5) the July 1, 1975 date referred to in § 310.503 (d)(3), (f)(5), and (g) is extended to February 20, 1976. The regulations have been revised accordingly. The Commissioner concludes that there has been adequate discussion and notice of these requirements, and that the time periods established should not result in a hardship to any manufacturer.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 505, 701 (a), 52 Stat. 1052–1053, as amended, 1055 (21 U.S.C. 355, 371(a)), the Public Health Service Act (sec. 351, 58 Stat. 702, as amended (42 U.S.C. 262)), authority delegated to the Commissioner (21 CFR 2.120), and in cooperation with the Nuclear Regulatory Commission, Title 21 of the Code of Federal Regulations is amended as follows:

PART 201—LABELING

1. In Subpart D a new § 201.129 is added to read as follows:

§ 201.129 Drugs and devices; exemption for radioactive drugs for research use.

A radioactive drug intended for administration to human research subjects during the course of a research project intended to obtain basic research information regarding metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry (but not intended for immediate therapeutic, diagnostic, or similar purposes), under the conditions set forth in § 361.1 of this chapter, shall be exempt from section 502(f)(1) of the act if the packaging, label, and labeling are in compliance with § 361.1(f) of this chapter.

PART 310—NEW DRUGS

2. In § 310.3 add a new paragraph (n) to read as follows:

§ 310.3 Definitions and interpretations.

* * * * *

(n) The term "radioactive drug" means any substance defined as a drug in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term "radioactive drug" includes a "radioactive biological product" as defined in § 600.3(ee) of this chapter.

3. In § 310.503 revise paragraph (d) and add new paragraphs (f), (g), and (h), to read as follows:

§ 310.503 Requirements regarding certain radioactive drugs.

* * * * *

(d) (1) In view of the extent of experience with the isotopes listed in paragraph (c) of this section, the Nuclear Regulatory Commission and the Food and Drug Administration conclude that such isotopes should not be distributed under investigational-use labeling when

they are actually intended for use in medical practice.

(2) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (c) of this section, in the "chemical form" and intended for the uses stated, is terminated on March 3, 1972, except as provided in paragraph (d)(3) of this section.

(3) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (c) of this section, in the "chemical form" and intended for the uses stated, for which drug a new drug application or a "Notice of Claimed Investigational Exemption for a New Drug" was submitted prior to March 3, 1972, or for which biologic an application for product license or "Notice of Claimed Investigational Exemption for a New Drug" was submitted prior to March 3, 1972, is terminated either upon issuance of a nonapprovable notice for the new drug application or application for product license or termination of the "Notice of Claimed Investigational Exemption for a New Drug," or on February 20, 1976, whichever occurs first.

* * * * *

(f) (1) Based on its experience in regulating investigational radioactive pharmaceuticals, the Nuclear Regulatory Commission has compiled a list of reactor-produced isotopes for which it considers that applicants may reasonably be expected to submit adequate evidence of safety and effectiveness for use as recommended in appropriate labeling; such use may include, among others, the uses in this tabulation:

Isotope	Chemical form	Use
Fluorine 18	Fluoride	Bone imaging.
Indium-113m	Diethylenetriamine pentaacetic acid (DTPA).	Brain imaging; kidney imaging.
Do	Chloride	Placenta imaging; blood pool imaging.
Technetium 99m	Human serum albumin microspheres.	Lung imaging.
Do	Diethylenetriamine pentaacetic acid (8n).	Kidney imaging; kidney function studies.
Do	do	Brain imaging.
Do	Polyphosphates	Bone imaging.
Do	Technetated aggregated albumin (human).	Lung imaging.
Do	Disodium etidronate.	Bone imaging.

(2) In view of the extent of experience with the isotopes listed in paragraph (f)(1) of this section, the Nuclear Regulatory Commission and the Food and Drug Administration conclude that they should not be distributed under investigational-use labeling when they are actually intended for use in medical practice.

(3) Any manufacturer or distributor interested in continuing to ship in interstate commerce drugs containing the isotopes listed in paragraph (f)(1) of this section for any of the indications listed, shall submit, on or before August 25, 1975 to the Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852, a new drug application or a "Notice of Claimed Investigational Exemption for a New Drug" for each such drug for which the manufacturer or distributor does not have an approved new drug application pursuant to section 505(b) of the act. If the drug is a biologic, a "Notice of Claimed Investigation Exemption for a New Drug" or an application for a license under section 351 of the Public Health Service Act shall be submitted to the Bureau of Biologics, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20014, in lieu of any submission to the Bureau of Drugs.

(4) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (f)(1) of this section, in the "chemical form" and intended for the uses stated, is terminated August 25, 1975 except as provided in paragraph (f)(5) of this section.

(5) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (f)(1) of this section in the "chemical form" and intended for the uses stated, for which drug a new drug application or a "Notice of Claimed Investigational Exemption for a New Drug" was submitted to the Bureau of Drugs on or before August 25, 1975 or for which biologic an application for product license or "Notice of Claimed Investigational Exemption for a New Drug" was submitted to the Bureau of Biologics on or before August 25, 1975 is terminated either upon issuance of a nonapprovable notice for the new drug application or application for product license or termination of the "Notice of Claimed Investigational Exemption for a New Drug," or on February 20, 1976 whichever occurs first.

(g) The exemption referred to in paragraph (a) of this section, as applied to any drug intended solely for investigational use as part of a research project, which use had been approved on or before July 25, 1975 in accordance with 10 CFR 35.11 (or equivalent regulation of an Agreement State) is terminated on February 20, 1976 if the manufacturer of such drug or the sponsor of the investigation of such drug submits on or before August 25, 1975 to the Food and Drug Administration, Bureau of Drugs, HFD-150, 5600 Fishers Lane, Rockville, MD 20852, the following information:

(1) The research project title;

(2) A brief description of the purpose of the project;

(3) The name of the investigator responsible;

(4) The name and license number of the institution holding the specific license under 10 CFR 35.11 (or equivalent regulation of an Agreement State);

(5) The name and maximum amount per subject of the radionuclide used;

(6) The number of subjects involved; and

(7) The date on which the administration of the radioactive drugs is expected to be completed.

(h) The exemption referred to in paragraph (a), as applied to any drug not referred to in paragraphs (d), (f), and (g) of this section, is terminated after August 25, 1975.

PART 312—NEW DRUGS FOR INVESTIGATIONAL USE

4. In § 312.1, amend paragraph (a)(2) in Form FD-1571 by adding a new item 6.d and two new sentences to item 10.a and delete in its entirety, effective August 25, 1975, the "Note" regarding an order of the Commissioner of Food and Drugs published in the FEDERAL REGISTER on January 8, 1963 (28 FR 183), as it appears at the end of § 312.1, to read as follows:

§ 312.1 Conditions for exemption of new drugs for investigational use.

(a) * * *

(2) * * *

FORM FD-1571

* * * * *

6. * * *

d. If the drug is a radioactive drug, sufficient data must be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed dose upon administration to a human being.

* * * * *

10.* * *

a. * * *

If a drug is a radioactive drug, the clinical pharmacology phase must include studies which will obtain sufficient data for dosimetry calculations. These studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material.

* * * * *

PART 361—PRESCRIPTION DRUGS FOR HUMAN USE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED: DRUGS USED IN RESEARCH

5. Add a new Part 361, consisting at this time of one section, to read as follows:

AUTHORITY: Federal Food, Drug, and Cosmetic Act, Sec. 505, 701(a), 52 Stat. 1052-1053, as amended, 1055 (21 U.S.C. 355, 371(a)); Public Health Service Act, Sec. 351, 58 Stat. 702, as amended (42 U.S.C. 262).

§ 361.1 Radioactive drugs for certain research uses.

(a) Radioactive drugs (as defined in § 310.3(n) of this chapter) are generally recognized as safe and effective when administered, under the conditions set forth in paragraph (b) of this section, to human research subjects during the course of a research project intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial). Certain basic research studies,

e.g., studies to determine whether a drug localizes in a particular organ or fluid space and to describe the kinetics of that localization, may have eventual therapeutic or diagnostic implications, but the initial studies are considered to be basic research within the meaning of this section.

(b) The conditions under which use of radioactive drugs for research are considered safe and effective are:

(1) *Approval by Radioactive Drug Research Committee.* A Radioactive Drug Research Committee, composed and approved by the Food and Drug Administration in accordance with paragraph (c) of this section, has determined, in accordance with the standards set forth in paragraph (d) of this section, that:

(i) The pharmacological dose is within the limits set forth in paragraph (b) (2) of this section;

(ii) The radiation dose is within the limits set forth in paragraph (b) (3) of this section;

(iii) The radiation exposure is justified by the quality of the study being undertaken and the importance of the information it seeks to obtain;

(iv) The study meets the other requirements set forth in paragraph (d) of this section regarding qualifications of the investigator, proper licensure for handling radioactive materials, selection and consent of reserach subjects, quality of radioactive drugs used, research protocol design, reporting of adverse reactions, and approval by an appropriate Institutional Review Committee; and

(v) The use of the radioactive drug in human subjects has the approval of the Radioactive Drug Research Committee.

(2) *Limit on pharmacological dose.* The amount of active ingredient or combination of active ingredients to be administered shall be known not to cause any clinically detectable pharmacological effect in human beings. If the same active ingredients (exclusive of the radionuclide) are to be administered simultaneously, e.g., under a "Notice of Claimed Investigational Exemption for a New Drug" or for a therapeutic use in accordance with labeling for a drug approved under Part 314 of this chapter, the total amount of active ingredients including the radionuclide shall be known not to exceed the dose limitations applicable to the separate administration of the active ingredients excluding the radionuclide.

(3) *Limit on radiation dose.* The amount of radioactive material to be administered shall be such that the subject receives the smallest radiation dose with which it is practical to perform the study without jeopardizing the benefits to be obtained from the study.

(i) Under no circumstances may the radiation dose to an adult research subject from a single study or cumulatively from a number of studies conducted within 1 year be generally recognized as safe if such dose exceeds the following:

Whole body, active blood-forming organs, lens of the eye, and gonads:	*Rems*
Single dose	3
Annual and total dose commitment	5
Other organs:	
Single dose	5
Annual and total dose commitment	15

(ii) For a research subject under 18 years of age at his last birthday, the radiation dose shall not exceed 10 percent of that set forth in paragraph (b) (3) (i) of this section.

(iii) All radioactive material included in the drug either as essential material or as a significant contaminant or impurity shall be included when determining the total radiation doses and dose commitments. Radiation doses from x-ray procedures that are part of the research study (i.e., would not have occurred but for the study) shall also be included. The possibility of followup studies shall be considered for inclusion in the dose calculations.

(iv) Numerical definitions of dose shall be based on an absorbed fraction method of radiation absorbed dose calculation, such as the system set forth by the Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine, or the system set forth by the International Commission on Radiological Protection.

(c) A Radioactive Drug Research Committee, in order to comply with paragraph (b) (1) of this section, shall be composed, shall function, and shall obtain and maintain approval of the Food and Drug Administration in conformity with the following:

(1) *Membership.* A Radioactive Drug Research Committee shall consist of at least five individuals. Each committee shall include the following three individuals: (i) A physician recognized as a specialist in nuclear medicine, (2) a person qualified by training and experience to formulate radioactive drugs, and (3) a person with special competence in radiation safety and radiation dosimetry. The remainder of the committee shall consist of individuals qualified in various disciplines pertinent to the field of nuclear medicine (e.g., radiology, internal medicine, clinical pathology, hematology, endocrinology, radiation therapy, radiation physics, radiation biophysics, health physics, and radiopharmacy). Membership shall be sufficiently diverse to permit expert review of the technical and scientific aspects of proposals submitted to the committee. The addition of consultants in other pertinent medical disciplines is encouraged. A Radioactive Drug Research Committee shall be either associated with a medical institution operated for care of patients and with sufficient scientific expertise to allow for selection of committee members from its faculty, or with a committee established by a State authority to provide advice on radiation health matters. Joint committees involving more than one medical institution which have been established in order to achieve a high level and diversity of experience will be acceptable. The Director of the Bureau of Drugs may modify any of the foregoing requirements in a particular situation where alternative factors provide substantially the same composition and association.

(2) *Function.* Each Radioactive Drug Research Committee shall select a chairman, who shall sign all applications, minutes, and reports of the committee. Each committee shall meet at least once each quarter in which research activity has been authorized or conducted. A quorum consisting of more than 50 percent of the membership must be present with appropriate representation of the required fields of specialization. Minutes shall be kept and shall include the numerical results of votes on protocols involving use in human subjects. No member shall vote on a protocol in which he is an investigator.

(3) *Reports.* Each Radioactive Drug Research Committee shall submit an annual report on or before January 31 of each year to the Food and Drug Administration, Bureau of Drugs, HFD–150, 5600 Fishers Lane, Rockville, MD 20852. The annual report shall include the names and qualifications of the members of, and of any consultants used by, the Radioactive Drug Research Committee, and, for each study conducted during the preceding year, a summary of information presented in the following format:

REPORT ON RESEARCH USE OF RADIOACTIVE DRUG

1. Title of the research project.
2. Brief description of the purpose of the research project.
3. Name of the investigator responsible.
4. Pharmacological dose:
   a. Active ingredients.
   b. Maximum amount administered per subject.
5. Name of the radionuclide(s) used, including any present, as significant contaminants or impurities.
6. Radiation absorbed dose. Give the methods by which radiation dose commitment was estimated, such as by calculation, by in vivo measurements, by uptake excretion, or by other methods. For each subject; provide:
   a. Age, sex.
   b. Amount of each radionuclide administered.
   c. Estimated absorbed dose per single administration of radioactive drug, expressed as whole body, active blood-forming organs, lens of the eye, gonads, and other organ dose.
   d. If more than one administration of a radioactive drug per subject, cumulative radiation dose and dose commitment, expressed as whole body, active blood-forming organs, lens of the eye, gonads, and other organ doses from the administered radionuclides.
7. A claim of confidentiality, if any.

NOTE: Contents of this report are available for public disclosure unless confidentiality is requested by the investigator and it is adequately shown by the investigator that the report constitutes a trade secret or confidential commercial information as defined in 21 CFR 4.61.

Investigator

Chairman, Radiation Safety Committee

At any time a proposal is approved which involves exposure either of more than 30 research subjects, or of any research subject under 18 years of age, the committee shall immediately submit to the Food and Drug Administration a special summary of information in the format shown in this paragraph. Contents of these reports are available for public disclosure, unless confidentiality is requested by the investigator and it is adequately shown by the investigator that the report constitutes a trade secret or confidential commercial information as defined in § 4.61 of this chapter.

(4) *Approval.* Each Radioactive Drug Research Committee shall be specifically approved by the Bureau of Drugs of the Food and Drug Administration. Applications shall be submitted to the Food and Drug Administration, Bureau of Drugs, HFD–150, 5600 Fishers Lane, Rockville, MD 20852, and shall contain the names and qualifications of the members of the committee, and a statement that the committee agrees to comply with the requirements set forth in this section. Approval shall be based upon an assessment of the qualifications of the members of the committee, and the assurance that all necessary fields of expertise are covered. Approval of a committee may be withdrawn at any time for failure of the committee to comply with any of the requirements of this section. Approval of a committee shall remain effective unless and until the FDA withdraws such approval. Changes in membership and applications for new members shall be submitted to the Food and Drug Administration as soon as, or before, vacancies occur on the committee.

(5) *Monitoring.* The Food and Drug Administration shall conduct periodic reviews of approved committees. Monitoring of the activities of the committee shall be conducted through review of its annual report, through review of minutes and full protocols for certain studies, and through on-site inspections.

(d) In making the determinations required in paragraph (b)(1) of this section, a Radiation Safety Committee shall consider the following requirements and assure that each is met:

(1) *Radiation dose to subjects.* To assure that the radiation dose to research subjects is as low as practicable to perform the study and meet the criteria of § 361.1(b)(3), the Radioactive Drug Research Committee shall require that:

(i) The investigator provide absorbed dose calculations based on biologic distribution data available from published literature or from other valid studies.

(ii) The investigator provide for an acceptable method of radioassay of the radioactive drug prior to its use to assure that the dose calculations actually reflect the administered dose.

(iii) The radioactive drug chosen for the study has that combination of half-life, types of radiations, radiation energy, metabolism, chemical properties, etc., which results in the lowest dose to the whole body or specific organs with which it is possible to obtain the necessary information.

(iv) The investigator utilize adequate and appropriate instrumentation for the detection and measurement of the specific radionuclide.

(2) *Pharmacological dosage.* To determine that the amount of active ingredients to be administered does not exceed the limitations set forth in paragraph (b)(2) of this section, the committee shall require that the investigator provide pharmacological dose calculations based on data available from published literature or from other valid human studies.

(3) *Qualifications of investigators.* Each investigator shall be qualified by training and experience to conduct the proposed research studies.

(4) *License to handle radioactive materials.* The responsible investigator or institutions shall, in the case of reactor-produced isotopes, be licensed by the Nuclear Regulatory Commission or Agreement State to possess and use the specific radionuclides for research use or be a listed investigator under a broad license, or in the case of non-reactor-produced isotopes, be licensed by other appropriate State or local authorities, when required by State or local law, to possess and use the specific radionuclides for research use.

(5) *Human research subjects.* Each investigator shall select appropriate human subjects and shall obtain the consent of such human beings or their representatives in accordance with § 310.102 of this chapter. The research subjects shall be at least 18 years of age and legally competent. Exceptions are permitted only in those special situations when it can be demonstrated to the committee that the study presents a unique opportunity to gain information not presently available and requires the use of research subjects less than 18 years of age and is without significant risk to the subject. Studies involving minors shall be supported with review by qualified pediatric consultants to the Radioactive Drug Research Committee. Each female research subject of child-bearing potential shall state in writing that she is not pregnant, or, on the basis of a pregnancy test, be confirmed as not pregnant before she may participate in any study.

(6) *Quality of radioactive drug.* The radioactive drug used in the research study shall meet appropriate chemical, pharmaceutical, radiochemical, and radionuclidic standards of identity, strength, quality, and purity as needed for safety and be of such uniform and reproducible quality as to give significance to the research study conducted. The Radioactive Drug Research Committee shall determine that radioactive materials for parenteral use are prepared in sterile and pyrogen-free form.

(7) *Research protocol.* No matter how small the amount of radioactivity, no study involving administration of a radioactive drug, as defined in § 310.3(n) of this chapter, to research subjects under this section, shall be permitted unless the Radioactive Drug Research Committee concludes, in its judgment, that scientific knowledge and benefit is likely to result from that study. Therefore, the protocol shall be based upon a sound rationale derived from appropriate animal studies or published literature and shall be of sound design such that information of scientific value may result. The radiation dose shall be both sufficient and no greater than necessary to obtain valid measurement. The projected number of subjects shall be sufficient but no greater than necessary for the purpose of the study. The number of subjects shall also reflect the fact that the study is intended to obtain basic research information referred to in paragraph (a) of this section and not intended for immediate therapeutic, diagnostic or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial).

(8) *Adverse reactions.* The investigator shall immediately report to the Radioactive Drug Research Committee all adverse effects associated with the use of the radioactive drug in the research study. All adverse reactions probably attributable to the use of the radioactive drug in the research study shall be immediately reported by the Radioactive Drug Research Committee to the Food and Drug Administration, Bureau of Drugs, HFD–150, 5600 Fishers Lane, Rockville, MD 20852.

(9) *Approval by Institutional Review Committee.* The investigator shall obtain the review and approval of an Institutional Review Committee which conforms to the requirements of 45 CFR Part 46.

(e) The results of any research conducted pursuant to this section as part of the evaluation of a drug pursuant to § 312.1 of this chapter shall be included in the submissions required under § 312.1 of this chapter.

(f) A radioactive drug prepared, packaged, distributed, and primarily intended for use in accordance with the requirements of this section shall be exempt from section 502(f)(1) of the act and §§ 201.5 and 201.100 of this chapter if the packaging, label, and labeling are in compliance with Federal, State, and local law regarding radioactive materials and if the label of the immediate container and shielded container, if any, either separate from or as part of any label and labeling required for radioactive materials by the Nuclear Regulatory Commission or by State or local radiological health authorities bear the following:

(1) The statement "Caution: Federal law prohibits dispensing without prescription";

(2) The statement "To be administered in compliance with the requirements of Federal regulations regarding radioactive drugs for research use (21 CFR 361.1)";

(3) The established name of the drug, if any;

(4) The established name and quantity of each active ingredient;

(5) The name and half-life of the radionuclide, total quantity of radioactivity in the drug product's immediate con-

tainer, and amount of radioactivity per unit volume or unit mass at a designated referenced time;

(6) The route of administration, if it is for other than oral use;

(7) The net quantity of contents;

(8) An identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug;

(9) The name and address of the manufacturer, packer, or distributor;

(10) The expiration date, if any;

(11) If the drug is intended for parenteral use, a statement as to whether the contents are sterile;

(12) If the drug is for other than oral use, the names of all inactive ingredients, except that:

(i) Trace amounts of harmless substances added solely for individual product identification need not be named.

(ii) If the drug is intended for parenteral use, the quantity or proportion of all inactive ingredients, except that ingredients added to adjust pH or to make the drug isotonic may be declared by name and a statement of their effect; if the vehicle is water for injection, it need not be named. *Provided, however,* That in the case of containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information, the information required by paragraph (f) (1) and (12) of this section may be placed on the shielded container only.

Effective date: This regulation shall become effective on July 25, 1975. This date is necessary because of the various effective dates set forth for specific changes relating to the transitional regulation of radioactive new drugs from the Nuclear Regulatory Commission to the Food and Drug Administration, and the need for this regulation to be in force as soon as possible so that there will be regulatory control over the safety and effectiveness of all radioactive drugs.

(Secs. 505, 701(a), 52 Stat. 1052-1053, as amended, 1055 (21 U.S.C. 355, 371(a)); the Public Health Service Act (sec. 351, 58 Stat. 702, as amended (42 U.S.C. 262))

Dated: July 18, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.75-19316 Filed 7-24-75;8:45 am]

[Docket No. 75N-0068]

RADIOACTIVE BIOLOGICAL PRODUCTS

Reassignment of Responsibility

By this regulation, the Commissioner of Food and Drugs is reassigning responsibility within the Food and Drug Administration for regulating radioactive biological products from the Bureau of Biologics to the Bureau of Drugs. As a result of this reassignment, manufacturers of radioactive biological products will be required to comply with the requirements for drugs (including submitting new drug applications and periodic reports) for such products in lieu of the requirements for biological products (including submitting establishment and product license applications). All future correspondence and submissions regarding radioactive biological products shall be directed to the Bureau of Drugs. This order becomes effective August 25, 1975.

The Division of Biologics Standards (DBS) was transferred from the National Institutes of Health to the Food and Drug Administration (FDA) and renamed the Bureau of Biologics (notice of which was published in the FEDERAL REGISTER of June 29, 1972 (37 FR 12865)). As the first step in effecting an orderly transfer, the DBS was appended to the FDA as a Bureau without any realignment of overlapping or related functions that had developed between DBS and FDA based on historical, statutory, and organizational distinctions.

Since the transfer of DBS to FDA, the Commissioner has reviewed those activities that historically have been conducted by DBS and the Bureau of Biologics under section 351 of the Public Health Service Act as well as those conducted by the FDA, principally the Bureau of Drugs, under the Federal Food, Drug, and Cosmetic Act. He concludes that there is a need for some reassignment of activities regarding radioactive drugs between the Bureau of Biologics and the Bureau of Drugs to provide uniformity in processing and a focal point for action within FDA for this category of products.

The Bureau of Biologics currently exercises primary control over those radioactive drugs which contain a biological product in addition to a radionuclide; such products have been subject to licensure under section 351 of the Public Health Service Act. The Bureau of Drugs regulates all other radioactive drugs.

Radioactive biological products, however, in addition to being subject to section 351 of the Public Health Service Act, are also "drugs" and "new drugs" as those terms are defined in section 201 (g) and (p), respectively, of the Federal Food, Drug, and Cosmetic Act and are therefore subject to the drug provisions of the Federal Food, Drug, and Cosmetic Act, including the new drug provisions. Recognizing this dual jurisdiction over biological products, the Department of Health, Education, and Welfare decided many years ago (prior to the transfer of DBS to FDA) that to market a biological product a manufacturer should not be required to submit both a license application under section 351 of the Public Health Service Act and a new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act. To require such dual submissions would have resulted in unnecessary duplication of effort, both by the manufacturer and by the Department. Instead, to avoid such duplication, only license applications under section 351 of the Public Health Service Act would be required. The new drug regulations (21 CFR 310.4) were amended to state that a new drug would not be deemed subject to the new drug provisions of the Federal Food, Drug, and Cosmetic Act if it is a drug licensed as a biological product under the Public Health Service Act.

The Commissioner now concludes that, since radioactive drugs, including radioactive biological products, are drugs in which the radioactive component is of primary interest, all radioactive drugs should be regulated through only one Bureau to achieve uniformity of treatment through a single contact point. The Commissioner further concludes that the Bureau of Drugs should be responsible for all radioactive drugs because of its existing organizational structure and staffing. The Bureau of Biologics will provide the Bureau of Drugs needed expertise with respect to the biological component of radioactive biological products and will test all samples of such products that are submitted in support of new drug applications.

As a result of this decision to transfer responsibility for radioactive biological products from the Bureau of Biologics to the Bureau of Drugs, all future applications and submissions for radioactive drugs, including radioactive biological products, shall be in the format and follow the procedures prescribed in 21 CFR Part 314. For radioactive biological products, the new drug application prescribed in 21 CFR 314.1 will be deemed to constitute the establishment and product license applications required for biological products; approval of the new drug application shall be in lieu of issuing a product and an establishment license. The requirement to submit new drug applications is not expected to impose any hardship on manufacturers of radioactive biologicals. The evidence required to establish safety and effectiveness are essentially the same for both biological products and new drugs. These are firms now holding biological product licenses for radioactive biological products, and all of them also manufacture other products requiring new drug applications. The impact on the regulated industry should, therefore, not be significant. The Commissioner advises that, if any person is preparing a biological product license application, he should submit it within 30 days in order to have it processed in that form.

In addition, compliance with the provisions of 21 CFR Part 314 shall be deemed to constitute compliance with the provisions of Subchapter F, the biological product regulations, unless the Commissioner makes a determination that a particular regulation in Subchapter F shall be applicable to radioactive drugs containing a biological product. Application of a Subchapter F regulation will only be made when the Commissioner concludes that it is necessary to assure the safety or effectiveness of the product, is not duplicative of the requirements in Part 314, and is to assure the same degree of regulatory control currently exercised over such products. The Commissioner has reviewed the provisions of Subchapter F and concludes at this time that the provisions of § 610.2 Requests for samples and protocols; official release shall remain applicable to radioactive drugs containing

a biological product. Appropriate changes have been made to this section to reflect that the Director of the Bureau of Drugs may use this section for radioactive drugs containing a biological product when it is deemed necessary for the safety, purity, or potency of the product.

To effect the transfer of responsibility, amendments must be made in 21 CFR Parts 310, 312, 314, 600, 601, and 610. In Part 310, § 310.4 provides the exemption, previously discussed, that a licensed biological product need not also be subject to an approved new drug application; that section is amended to exclude radioactive biological products from this exemption. In Part 312, § 312.1(g) currently provides that a "Notice of Claimed Investigational Exemption for a New Drug" (IND) for a biological product be submitted to the Bureau of Biologics; this section is amended to provide that an IND for a radioactive biological product be submitted to the Bureau of Drugs. In Part 314, § 314.110(a)(7) provides that a new drug application will be refused for filing if the drug is subject to licensing under the Public Health Service Act; this section is amended to permit filing of a new drug application for a radioactive biological product. Part 600 is amended in § 600.3 to include a definition of a radioactive biological product, which is defined as a biological product labeled with a radionuclide or a biological product intended solely to be labeled with a radionuclide. (Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is issuing a final regulation on radioactive drugs which includes a definition of "radioactive drug" in Part 310; this definition cross-references the new definition in Part 600.) In Part 601, § 601.2 currently outlines the procedures for filing applications for establishment and product licenses or biologics; this section is amended to provide that radioactive biological products shall be covered by new drug applications and not by biological product licenses. Part 610 is amended as discussed above.

These changes are prospective in nature. Every biological product licensed prior to July 1, 1972, is currently under review for safety, effectiveness, and appropriate labeling, as described in 21 CFR 601.25. The product license for such a radioactive biological product, together with portions of the establishment license relevant to the requirements for a new drug application, now constitutes an approved new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act. Any such products, even through new subject to new drug applications, will remain subject to the biological product review, because they were licensed as biological products before July 1, 1972. Those products which are found to be unsafe, or ineffective, or misbranded will be subject to regulatory action. Those which are determined to be safe, effective and not misbranded may continue to be marketed; in addition, the conditions under which an identical, similar or related product may be introduced to the market (i.e., full new drug application, abbreviated new drug applications, or other conditions) will be determined at that time.

A new drug application does not have to be submitted for any radioactive biological product licensed after July 1, 1972, and before the effective date of this order. The product license for such a radioactive biological product, together with portions of the establishment license relevant to the requirements for a new drug application, now constitutes an approved new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act.

Any radioactive biological product for which a license application is pending on the effective date of this order will be processed and approved or disapproved as submitted. Again, no new drug application need be submitted for these products. If the product is found acceptable for licensure, it will be approved as a new drug application in lieu of issuance of a product license.

Future changes in all approved radioactive biological products will be subject to supplemental new drug applications (21 CFR 314.8) rather than amendments to the license. Likewise, all radioactive biological products are subject to the records and reports requirements of 21 CFR 310.300 after the effective date of this section.

Every current "Notice of Claimed Investigational Exemption for a New Drug" for a radioactive biological product will be transferred to the Bureau of Drugs. Any amendments of or supplements to any such notice, and all progress reports regarding such notice, shall be filed in the future with the Bureau of Drugs. Any new "Notice of Claimed Investigational Exemption for a New Drug" for a radioactive biological product shall be submitted directly to the Bureau of Drugs.

For all radioactive biological products, including any subject to pending application for licensure on the effective date of this order, all correspondence, "Notices of Claimed Investigational Exemption for a New Drugs," and original and supplemental new drug applications shall be submitted to the Division of Oncology and Radiopharmaceutical Drug Products (HFD–150), Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852. All samples of radioactive biological products submitted in support of a new drug application shall, when notified by the Bureau of Drugs, be sent directly to the Bureau of Biologics, Food and Drug Administration, Bldg. 29A, 8800 Rockville Pike, Bethesda, MD 20014.

The Commissioner notes that the labeling standards under Part 610, Subpart G, of Subchapter F will no longer apply to radioactive biological products; instead, the requirements of 21 CFR Part 201 of Subchapter C will be applicable. In particular, this means that the manufacturer's license number appearing on the container and package labels (21 CFR 610.60(a)(2) and 610.61(b)) is no longer required. To permit an orderly and economical transition regarding labels and labeling of marketed products, the Commissioner will delay the effective date on which marketed radioactive biological products must comply with the requirements of Part 201 until the date on which new labels and/or labeling is printed by the manufacturer of such product, or July 26, 1976, whichever occurs first.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 505, 701(a), 52 Stat. 1052–1053 as amended, 1055 (21 U.S.C. 355, 371(a)), the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)), and under authority delegated to the Commissioner (21 CFR 2.120), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

PART 310—NEW DRUGS

1. In Subpart A by revising § 310.4 to read as follows:

§ 310.4 Biologics; products subject to license control.

(a) Except for radioactive biological products intended for human use, a new drug shall not be deemed to be subject to section 505 of the act if it is a drug licensed under the Public Health Service Act of July 1, 1944 (58 Stat. 682, as amended (42 U.S.C. 201 et seq.)) or under the animal virus, serum, and toxin law of March 4, 1913 (37 Stat. 832 (21 U.S.C. 151 et seq.)).

(b) A radioactive biological product (as defined in § 600.3(ee) of this chapter) intended for human use is subject to section 505 of the act. Any license for such a radioactive biological product which is issued under the Public Health Service Act of July 1, 1944 (58 Stat. 682, as amended (42 U.S.C. 201 et seq.)) and which has not been revoked or suspended as of August 25, 1975 shall constitute an approved new drug application in effect under the same terms and conditions as set forth in such license and such portions of the establishment license relating to such product, which include data and information required under Part 314 of this chapter for a new drug application. Any such radioactive biological product for which licensure under the Public Health Service Act is pending on August 25, 1975 shall, upon determination that it is acceptable for licensure, be approved as a new drug application in lieu of issuance of a biological product license.

PART 312—NEW DRUGS FOR INVESTIGATIONAL USE

2. In § 312.1 by revising paragraph (g) to read as follows:

§ 312.1 Conditions for exemption for new drugs for investigational use.

* * * * *

(g) A "Notice of Claimed Investigational Exemption for a New Drug" which pertains to a product subject to the licensing provisions of the Public Health Service Act of July 1, 1944 (58 Stat. 682, as amended (42 U.S.C. 201 et seq.)) shall

be submitted initially to the Director, Bureau of Biologics, 8800 Rockville Pike, Bethesda, MD 20014. Radioactive biological products for human use are not deemed to be subject to the licensing provisions of the Public Health Service Act (see § 310.4 of this chapter) and a "Notice of Claimed Investigational Exemption for a New Drug" which pertains to radioactive biological products shall be submitted to the Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, 5600 Fishers Lane, Rockville, MD 20852. Amendments of or supplements to such notice, and progress reports, consultations, or other communications with regard to the investigation shall be directed to the same office to which the original notice was sent. A sponsor for a "Notice of Claimed Investigational Exemption for a New Drug" submitted to the Bureau of Biologics shall substitute in reading this section "Bureau of Biologics" for "Bureau of Drugs" wherever it appears.

* * * * *

PART 314—NEW DRUG APPLICATIONS

3. In § 314.110 by revising paragraph (a) (7) to read as follows:

§ 314.110 Reasons for refusing to file applications.

(a) * * *

(7) The new drug is a drug, other than a radioactive biological product (as defined in § 600.3(ee) of this chapter) intended for human use, subject to licensing under the Public Health Service Act of July 1, 1944 (58 Stat. 682, as amended (42 U.S.C. 201 et seq.)).

* * * * *

PART 600—GENERAL PROVISIONS

4. In § 600.3 by adding a new paragraph (ee) to read as follows:

§ 600.3 Definitions.

* * * * *

(ee) "Radioactive biological product" means a biological product which is labeled with a radionuclide or intended solely to be labeled with a radionuclide.

PART 601—LICENSING

5. In § 601.2 by redesignating the present text as paragraph (a) *General* and adding at the end a new sentence and by adding a new paragraph (b). As revised, § 601.2 reads as follows:

§ 601.2 Applications for establishment and product licenses; procedures for filing.

(a) *General.* To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Bureau of Biologics, on forms prescribed for such purpose, and in the case of an application for a product license, shall submit data derived from laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of the labels enclosures and containers proposed to be used for the product. An application for license shall not be considered as filed until all pertinent information and data shall have been received from the manufacturer by the Bureau of Biologics. In lieu of the procedures described in this paragraph, applications for radioactive biological products shall be handled as set forth in paragraph (b) of this section.

(b) *Radioactive biological products.* In lieu of submitting an establishment and product license for the manufacture of a radioactive biological product, as defined in § 600.3(ee) of this chapter, the manufacturer of such a product shall submit a new drug application to the Director, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852, on form FD-356(H) as set forth in § 314.1(c)(2) of this chapter. For such products, the approval of the new drug application will be in lieu of issuing a product and an establishment license. Compliance with the provisions of Part 314 of this chapter shall be deemed to constitute compliance with the provisions of Subchapter 4 of this chapter unless the Commissioner makes a determination that a particular regulation from Subchapter F shall be applicable to radioactive drugs containing a biological product, e.g., § 610.2 of this chapter.

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

6. In § 610.2 by redesignating the present text as paragraph (a) *General* and revising it, and by adding a new paragraph (b). As revised, § 610.2 reads as follows:

§ 610.2 Request for samples and protocols; official release.

(a) *General.* Samples of any lot of any licensed product, except for radioactive biological products, together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Bureau of Biologics. Upon notification by the Director, Bureau of Biologics, a manufacturer shall not distribute a lot of a product until the lot is released by the Director, Bureau of Biologics: *Provided*, That the Director, Bureau of Biologics, shall not issue such notification except when deemed necessary for the safety, purity, or potency of the product.

(b) *Radioactive biological products.* Samples of any lot of a radioactive biological product, as defined in § 600.3(ee) of this chapter, together with the protocols showing results of applicable tests, may at any time be required to be sent to the Food and Drug Administration for official release. Upon notification by the Director, Bureau of Drugs, a manufacturer shall not distribute a lot of a radioactive biological product until the lot is released by the Director, Bureau of Drugs: *Provided*, That the Director, Bureau of Drugs shall not issue such notification except when deemed necessary for the safety, purity, or potency of the product.

Since these changes concern internal reassignment of activities and will promote uniform handling of all radioactive drug products, the Commissioner finds that the changes covered by this order are such that, under 5 U.S.C. 553, the notice and comment procedure for rule making are unnecessary and are not prerequisites to this promulgation. In reaching this decision, the Commissioner has considered the facts that less than ten firms currently hold biological product licenses for radioactive biological products, and that all of these firms also hold approved new drug applications. The Commissioner also advises that any person currently preparing a biological product license for a radioactive biological product may submit it within 30 days and thereafter will not be required to resubmit a new drug application for the product.

Interested persons may, however, on or before September 23, 1975, file with the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852, written comments in quintuplicate on any portion of the order. Comments received will be available for public inspection at the office noted above during working hours, Monday through Friday. Any changes in this order justified by such comments will be the subject of a further order amending the specific regulations involved.

Effective date. This regulation shall be effective August 25, 1975, except for the requirements for labels and labeling of radioactive biological products. The labels and labeling of any marketed radioactive biological product must comply with the requirements of 21 CFR Part 201 on the date on which such labels and labeling are next printed or July 26, 1975, whichever occurs first.

(Secs. 505, 701(a) 52 Stat. 1052–1053 as amended, 1055 (21 U.S.C. 355, 371(a)); sec. 351, 58 Stat. 702 as amended (42 U.S.C 262))

Dated: July 18, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[Docket No. 75N-0069]

RADIOACTIVE DRUGS, INCLUDING BIOLOGICAL PRODUCTS

Notice to Nuclear Pharmacies Regarding the Development of Proposed Regulations and Interim Enforcement Policy

This notice states the interim enforcement policy of the Commissioner of Food and Drugs regarding nuclear pharmacies until definitive regulations on this matter are issued by the Food and Drug Administration. Under the conditions set forth in this notice, the agency will not take regulatory action for the failure of a nuclear pharmacy to comply with the requirements of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act, except where such regulatory action is necessary to safeguard the public health.

Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is issuing a final regulation terminating the exemption from new drug requirements for radioactive drugs, including radioactive biological products. As a result, manufacturers and distributors of these products must comply with the requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and the regulations thereunder, including registration, drug listing, compliance with current good manufacturing practices, marketing under an approved new drug application or biological product license, research under the requirements for investigational drugs, and labeling and advertising requirements. In commenting on the proposal published in the FEDERAL REGISTER of July 29, 1974 (39 FR 27538), which preceded this final regulation, several persons inquired about the legal obligations of "nuclear pharmacies" under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act upon the effective date of the final regulation, especially insofar as these "nuclear pharmacies" may be deemed to be manufacturing or distributing these products other than as part of the compounding and dispensing of drugs in the ordinary practice of pharmacy.

Many radioactive drugs, including biological products, because of their short half-lives, must be prepared in the final dosage form shortly before they are to be used for diagnosis or treatment of disease in man. In addition, the preparation of radioactive drugs requires a special knowledge of radioactive materials, involves the use of special equipment and facilities, and, where reactor-produced radionuclides are involved, requires licensing by the Nuclear Regulatory Commission or an Agreement State. Certain pharmacies, referred to as "nuclear pharmacies," conduct operations which vary from repackaging or preparing radioactive drugs for administration to more extensive and complex manufacturing and compounding procedures. In most cases these nuclear pharmacies are affiliated with, or operated by, hospitals, medical groups, clinics, universities, medical schools, and public health agencies. Some of these pharmacies are not so affiliated, are privately owned, or are operated by several institutions on a cooperative basis. The radioactive drugs prepared by a nuclear pharmacy may be intended solely for use within the institution in which the pharmacy is located, or they may be prepared for distribution to other institutions. For example, a nuclear pharmacy in a university hospital may prepare radioactive drugs for distribution to other hospitals and clinics.

At present, pharmacies are subject to the misbranding and adulteration sections of the Federal Food, Drug, and Cosmetic Act and to the provisions of the Public Health Service Act regarding the licensing of biological products. If they engage in the manufacture of new drugs, they may also be subject to the new drug provisions of the Federal Food, Drug, and Cosmetic Act. Pharmacies are generally exempted under sections 510(g) and 704 (a) of the Federal Food, Drug, and Cosmetic Act from regulations regarding registration, drug listing, inspection, and compliance with current good manufacturing practices where their operations are in compliance with applicable local pharmacy laws and do not involve manufacturing procedures other than in the regular course of their business of dispensing or selling drugs at retail. Application of these rules and exemptions to nuclear pharmacies, which would be an immediate result of the final regulation referred to below, raises numerous complex issues or problems because of the unique nature of operations in nuclear pharmacies.

To clarify the obligations of nuclear pharmacies under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, the Food and Drug Administration is drafting regulations which will define those operations connected with the preparation of radioactive drugs and biological products which will be regarded as manufacturing procedures and not part of the practice of pharmacy. Nuclear pharmacies engaged in such operations will then be subject to regulations regarding registration, drug listing, inspection, new drug applications or biological product licenses, compliance with current good manufacturing practices, and related requirements. Operations not deemed to be manufacturing procedures will also be identified and will thereafter be treated as part of the practice of pharmacy. It is anticipated that these regulations will be proposed in the FEDERAL REGISTER in the near future. Interested persons will be given 60 days to comment on the proposed regulations and all such comments will be considered in the preparation and promulgation of the final regulation.

The Commissioner advises that, until the regulations outlined above are proposed and made final, the Food and Drug Administration will not take regulatory action for the failure of a nuclear pharmacy to comply with the requirements of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act, so long as the pharmacy (1) complies with applicable local laws regulating the practice of pharmacy and (2) is licensed, where applicable, by the Nuclear Regulatory Commission or an Agreement State to possess, use, or transfer radioactive drugs, except where the Commissioner determines that such regulatory action is necessary to safeguard the public health. The Food and Drug Administration is adopting this policy as an interim measure to avoid any disruption in the practice of nuclear pharmacy and nuclear medicine throughout the United States.

Dated: July 18, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

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